Applicant could not have submitted this response at an earlier date.

Applicant and his undersigned attorney wish to thank Examiner Hui for granting a telephone interview with the undersigned attorney. The telephone interview took place on 25 July 2006. During the interview the Examiner and the undersigned discussed how to define the patient to distinguish over SPELLACY et al, BUTTERWORTH et al and KAFRISSEN et al so that these references cannot be applied to establish that inherently the invention in the present method of use claims is disclosed in one or more of these prior art references. The undersigned proposed the following independent claim to Examiner Hui:

40. (New) A method of providing an antidote to a patient taking a gestagen hormone, who will suffer from an elevated level of plasma homocysteine, as a result of taking the gestagen hormone, which comprises the step of administering to the patient, along with the gestagen hormone, in unit dosage form, an amount of a plasma homocysteine reducing agent therapeutically effective to neutralize the plasma homocysteine elevating effect of the gestagen hormone.

The undersigned explained to Examiner Hui that the patient to whom the combination of B Vitamin and gestagen hormone is administered is a patient who has a normal plasma homocysteine level. The patients receiving treatment according to KAFRISSEN et al already have an elevated level of plasma homocysteine; see col., lines 44 to 55 and col. 5, lines 44 to 50. Thus the patient

treated according to the present invention is a different patient from the one treated according to KAFRISSEN et al.

The undersigned also stressed that there is no disclosure in SPELLACY et al or BUTTERWORTH et al of the invention proposed in claim 40. Each of these references is distinguishable from the process as Applicant proposed to claim it because each of these references shows administration of a gestagen hormone commencing prior to administration of folic acid or Vitamin B_6. Applicant alone administers both a gestagen hormone and a plasma homocysteine reducing agent, as an antidote to the plasma homocysteine increasing effect of the gestagen hormone, to a patient with a normal level of plasma homocysteine, to counteract the plasma homocysteine elevating effect of the gestagen hormone.

The Examiner indicated that for this argument to serve as a basis for distinguishing the presently claimed invention over KAFRISSEN et al, SPELLACY et al and BUTTERWORTH et al, the patient must be clearly defined in the claims as having a normal plasma homocysteine level at the commencement of treatment with the gestagen hormone and the plasma homocysteine agent. Examiner Hui agreed that Examples 1 and 2 and the description of the invention on pp 3 through 6 of the application state that the plasma homocysteine level of a patient taking a plasma homocysteine lowering agent such as folic acid along with a gestagen hormone will be lower than that of a patient who takes only the gestagen hormone. However, the Examiner did not believe that the description of the invention or the examples expressly indicate

that the patient treated according to the present invention has a normal plasma homocysteine level at the beginning of treatment with the gestagen hormone and the plasma homocysteine reducing agent. The matter of antecedent basis for the proposed attached claims must be considered.

Examiner Hui suggested that Applicant might overcome the problem of antecedent basis by providing the underlying data for Examples a) through e). The data would be provided in a Declaration Under 37 CFR 1.132. The Examiner in the case of Examples a) and b) wanted to see the data for the patients treated, both tested and control, showing that all patients at the beginning of the test had normal levels of plasma homocysteine, and that after the tests were completed, the group treated with the gestagen hormone had elevated plasma homocysteine levels whereas the control group did not. Examiner Hui emphasized that these data should be provided to show that the patients treated according to the present method have initially a normal plasma homocysteine level.

Next the Examiner indicated that the data in Examples c), d) and e) should be provided in the declaration to show that patients with initially normal plasma homocysteine levels who receive gestagen hormone therapy alone, suffer an increase in plasma homocysteine levels, whereas patients with initially normal plasma homocysteine levels who receive gestagen hormone therapy together with folic acid or Vitamin B6 maintain normal levels of plasma homocysteine.

Examiner Hui indicated that it is mandatory to include in the claims the limitation, in unit dosage form, in order to avoid the claim reading on a patient taking contraception or hormone replacement therapy, who also takes multivitamins or a vitamin supplement containing folic acid. The Examiner agreed that defining the claims as "an antidotal method" and words such as "counteracting" will improve Applicant's chance of obtaining a patent. The undersigned pointed to page 6, lines 3 to 14 of the present application as antecedent basis for the method of providing an antidote to a patient taking a gestagen hormone.

Examiner Hui did not promise that even if Applicant submits a claim such as claim40 as the independent claim, that the application will be allowed. The Examiner pointed out that the present application is under final rejection and so a Request for Continued Examination (RCE) must be filed and the new claims and arguments must be submitted in the RCE along with a report of the telephone interview and the Declaration Under 37 CFR 1.132. Once the RCE is filed, the Examiner reserved the right to perform another search of the prior art to check once again if there is any prior art even closer than SPELLACY et al, BUTTERWORTH et al and KAFRISSEN et al.

Applicant and his undersigned representative do appreciate the time and effort spent by Examiner Hui in conducting the interview with the Applicant's undersigned representative. Applicant is considering submission of claims in a continuation application that are consistent with the claims discussed during

the telephone interview. However, Applicant still believes that the present claims in the application are clear and definite and that these claims distinguish over the cited prior art and so Applicant still wants these claims to be considered by the Examiner, and if necessary by the Board of Appeals and Interferences. Thus Applicant is maintaining claims 9 through 12, 20, and 25 through 39 in the present application and is requesting reconsideration of the final rejection of those claims.

The Examiner has finally rejected claims 20, 26 through 28, 32 through 35, and 39 under 35 USC 112, second paragraph, as vague and indefinite. The Examiner maintains that claim 39 recites the limitation "for contraception" in line 3 and that there is improper antecedent basis in the claim for this limitation. Applicant disagrees since there is no definite article that is used in front of the expression "for contraception." Furthermore the fact that Applicant deleted in the previous amendment the term "for contraception" from claim 20 does not mean that Applicant is required to maintain this expression in claim 20 to provide antecedent basis for the term in claim 39.

The Examiner further maintains that it is not clear as to who is a healthy patient and whether a patient who suffers side effects such as headache or depression after taking a gestagen hormone is a healthy patient. Applicant asks that the Examiner reconsider his decision that these claims are vague and indefinite.

Applicant maintains that the term "otherwise healthy patient" in the case of treatment with hormone for contraception defines a patient who is healthy at the beginning of the hormone treatment and remains healthy in the course of the whole treatment. The term "otherwise healthy patient" in indications other than contraception means that apart from the indication of the hormone therapy the patient is healthy at the beginning of the hormone treatment and remains healthy in the course of the whole treatment. The fact that the patients according to the presently claimed invention remain healthy during the course of the whole treatment is supported by the following:

- The clinical trials disclosed in the present specification are qualified as Phase I trials, which, according to the professional rules, have to be suspended if clinically unexpected effects emerge;
- Also according to the professional rules, any such unexpected effect has to be reported in the summary.

Accordingly, the fact that the Applicant could complete his examinations evidences that his patients remained healthy in the course of the whole treatment. On page 8 in lines 20-21 it is specifically mentioned that "no undesired pregnancy or thromboembolic complication occurred". If any unexpected effect had occurred, it would have been mentioned in the specification.

Applicant's further remarks serve to both establish that the claims in the application are clear and definite in using the term - otherwise healthy patient - and that claims 9, 11, 20, 27,

32 through 36 and 39 are patentably distinguishable over the KAFRISSEN et al reference and so no rejection of any claim should be maintained as anticipated under 35 USC 102 or as obvious under 35 USC 103 in view of the KAFRISSEN et al.

The method of KAFRISSEN et al relates to patients who are afflicted with or predisposed to become afflicted with a disorder due to which they have to be steadily treated with folic acid. This means that the patients of KAFRISSEN et al have to be treated with folic acid independently of the hormone treatment. The present invention, however, relates to healthy patients who do not need folic acid treatment unless they take a gestagen hormone.
In other words, Kafrissen relates to patients for whom the incidence of certain disorders is higher than normal, while the same for the patients of the invention is non-higher than normal, i.e. normal.

The Examiner argues that an individual having a risk factor can be considered as healthy. Applicant does not agree with this opinion. Although it is agreed that "having the risk factors of a disease is not equal to having the disease itself, but, according to the Applicant, having the risk factors of a disease is not equal to being healthy. Accordingly, individuals can be sorted into three groups: healthy individuals, individuals having the risk factors of a disease, and ill individuals.

In addition, Applicant does not agree with the opinion of the Examiner (last paragraph, page 2), according to which "It is

not clear what patients or individuals would be considered "healthy"..., as the term "healthy" is a well-defined one.
In the following several references will be cited which evidence that the term "healthy" /"otherwise healthy" is clear and unambiguous for one skilled in the art and so the rejection of the claims under the second paragraph of 35 USC 112, should not be maintained:
According to the definition given in Adipex Phentermine Diet Pills, Diet Pills Glossory of Weight Loss Terms, (2002) (copy enclosed) appearing on the internet at (http://wvvw.adipex-phentermine-dietpills.comfdiet-pills-glossary.asp), "Health is defined as - The overall condition of an organism at a given time in regard to soundness of body or mind and freedom from disease or abnormality."

According to this definition, neither individuals with diseases nor individuals with other abnormalities (e.g. laboratorial abnormality due to which a predisposition can be detected) can be considered as healthy. In other words, those for whom a predisposition for a disease treatable with folic acid can be detected and those for whom no such detection is possible, cannot be both considered as healthy.

In addition, it is clear to a skilled person in the art that the examples of the present application describe clinical pharmaceutical trials (to carry out said trials also clinical-ethical permission had to be procured). Accordingly, the terms "healthy" or "otherwise healthy" have to be discussed in this

context, in other words, the question is what these terms mean for a skilled person if they are used in the description of a clinical trial.

According to a document of the National Institute of Health (USA), FAQs About Clinical Studies (copy enclosed), available over the internet at http://clinicaleenter.nih.gov/participate/faqaboutcs.shtml) on page 1, the definition of a healthy volunteer is given as follows:

3. What is a "healthy volunteer"? A volunteer subject with no known significant health problems who participates in research to test a new drug, device, or intervention is known as a "healthy volunteer" or "Clinical Research Volunteer." Accordingly, an individual who has medical problems to be treated with folic acid cannot be considered as healthy. In the case of the KAFRISSEN et al patent and of the presently claimed invention which go about treatment with folic acid the term "significant health problems" is to be understood as abnormalities (diseases or predisposition) to be treated with folic acid. It also follows that the other diseases mentioned by the Examiner are irrelevant, as, according to the present state of the art only folic acid deficiency and certain hyperhomocysteinemias can be treated with folic acid.

According to another document of the National Institute of Health, Patient Information Publications, NIH Clinical Center, (copy enclosed), available over the internet at

http://clinicaleenter.nih.gov/participate/-pdf/partners.pdf), the following information about healthy volunteers is given:
"We need to study healthy volunteers for several reasons: ... we need clinical research volunteers to help us define the limits of "normal"."
Accordingly, the group of healthy individuals forms the normal population, and the others can be defined in a way as KAFRISSEN et al does: "higher than normal".

The clinical trials disclosed in the present specification are qualified as Phase I trials. US FDA defines the term "healthy" in the case of Phase I Clinical trials carried out with healthy volunteers according to Phase 1 Clinical Studies, FDA Handbook (copy enclosed) available over the internet at (http://www.fda.gov/cder/handbook/phase1.htm).
"Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and may be conducted in patients, but are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness."

The next examples show what the term "healthy" means for a skilled person: FAQs on GCP, Clinical Trial Management, (copy enclosed) and available over the internet at (http://www.clininvent.com/clininvent/links/trial.html)

"What is the US FDA definition of a healthy volunteer?
US FDA guidance on General Considerations for Clinical Evaluation of Drugs discussed this issue. The term healthy suggests that volunteer should be free from abnormalities which could complicate interpretation of the experiment or which might increase the sensitivity of the volunteer to the toxic potential of the drug. Healthy volunteer is one who has no evidence of a clinical biochemical or investigational abnormality (based on physical examination, lab investigations (hematology, liver function, renal function, blood sugar, cholesterol, triglycerides) and x-ray chest ECG.

US FDA guidance for the industry, "General Considerations for the clinical evaluation of drugs" suggests the following investigations for phase I volunteers..

- CBC including platelet, urinalysis, BUN or creatinine, liver function, FBS or 2 hour postprandial sugar, ECG.
- Any other investigations as per the profile of the drug under investigation. For example, for a study on anti-platelet drug, it would be desirable to check BT, CT, PT in the volunteers. The importance of these tests is two fold. Volunteers should he free from abnormalities which would complicate the interpretation of experiment or which might increase the sensitivity of the subject to the toxic potential of the drug."

According to ABPI (Association of the British Pharmaceutical Industry), Impact of the EU Directive on Ethical Review& Phase 1 Studies, Vol. 14, No. 1, (Feb. 2003) (copy enclosed) and available

over the internet at http://archive.instituteofclinicalresearch.org/SMOSubCommittee/Phaseampact.pdfl healthy volunteers can be selected on the basis of full medical history and laboratory tests (page 2, paragraph 4). According to the homepage of the University of Surrey (Guildford), (copy enclosed) and available over the internet at (http://www.open.mis.surrev.ac.uldmisweb/modules/7431.htm) "Definition of a healthy volunteer (appropriate pre-study test, and considerations of the limits of 'normality' for laboratory data, cardiovascular data)."

Accordingly, the term "healthy" mentioned in the disclosure of the clinical trials in the present application means that at the beginning of the examinations (i.e. at the beginning of the hormone-vitamin treatment) <u>the participants of the trials had no such biochemical abnormality which would have required chronic folic acid treatment</u> (therapeutic or preventive). In other words, the meaning of the term "healthy" in the context of a clinical pharmaceutical trial is well-known for a skilled person: neither those who are afflicted with, nor those who are predisposed to become afflicted with a disorder due to which they require a continuous (preventive) treatment fall into this category. Obviously, the exact interpretation of the examinations would have been impossible if individuals had been involved who had been given folic acid not only to avoid the side effect of the hormone but they had been in need of folic acid treatment anyway.

Also according to Section 3.2.1. of a document of The European Agency for the Evaluation of Medicinal Products (EMEA), Note for Guidance on the Investigation of Bioavailability and Bioequivalence, (copy enclosed) and available over the internet at (http://www.emea.eu.int/pdfs/hum an/ewp/140198en.pdf)
healthy volunteers are selected on the basis of medical history and relevant laboratory tests. Therefore, those who are afflicted with, or those who are predisposed to become afflicted with a disorder due to which they require a continuous (preventive) treatment do not fall into this group, as the existing illness or the predisposition can be detected on the basis of the medical history and the relevant laboratory tests.

According to the definition given on the homepage of the International Psoriasis Community, a 501(c)(3) Organization, (copy enclosed) and appearing on the internet at
(http://www.psoriasissupport.org/ipc/default/pnint.asp?laug=1& cont=101)
the definition of a "healthy volunteer" is the same as given by the NIH (see above), which evidences the generic and accepted nature of the definition. This site also defines a "patient volunteer": "A volunteer subject with a known health problem, who participates in research to better understand, diagnose, treat, or cure a particular disease or condition."

On the basis of the definitions given for "healthy volunteer" and for "patient volunteer", the patients of KAFRISSEN et al and those of the present invention can be particularly well separated:

Healthy volunteer	Patient volunteer
no known .... health problem	known health problem
to test a new drug, device or intervention	to ... cure a particular disease or condition

Accordingly, for patient volunteers there is a disease to be treated (KAFRISSEN et al), for healthy volunteers there is no known health problem.
According to the information given on the home page of GlaxoSmithKline, (copy enclosed) available over the internet at http://wvvw.gsk.com/responsibility/cr_issues/ct_healthy_volunteers .htm
"volunteers normally do not have the disease or condition, ie they are healthy volunteers."
This example shows that the term "healthy" is interpreted by the second largest pharmaceutical company of the world, and, thus, by the skilled person, as including not only the absence of disease, but also the absence of other condition, such as absence of predisposition to become afflicted with a disorder.

According to the official homepage of the US FDA (http://www.fda.gov/) the term "otherwise healthy" is present in 929 documents of the US FDA. From said documents one is selected and enclosed as Enclosure 1 to evidence that the skilled person understands said term according to our interpretation detailed above.

The term "otherwise healthy patient" in indications other than contraception (e.g. in the case of hormone therapy), means that apart from the indication of the hormone therapy the patient is healthy (no other illnesses or predispositions). In Applicant's view this definition is well known to those skilled in the art. Applicant points to the literature citations included in Enclosure 1, which accompanies this response, wherein on page 2 it is disclosed in the US Food and Drug Administration, Equality in Clinical Trials Drugs and Gender, Judith Levine Willis, that a patient infected with HIV is categorized as otherwise healthy.

In response to the questions raised by the Examiner on page 2 of the office action concerning headache, it is submitted that headache is neither an illness nor a predisposition, but a symptom. A person having a headache may be healthy or may be ill. The question whether someone is healthy or not can be answered on the basis of results of examination and laboratory tests. Patients having normal results are healthy, and patients having abnormal results (e.g. higher than normal) are not healthy.

AS for the argumentation of the Examiner in paragraph 1of page 7 of the office action, the following is submitted: Comparing

males over the age of 65 with younger males, in the first group more individuals are afflicted with prostate cancer or more individuals have risk factors due to which they are predisposed to become afflicted with prostate cancer than in the second group. It does, however, not mean that all male individuals over the age of 65 are afflicted with or become predisposed to become afflicted with said disorder. The question whether someone is healthy or not can be answered on the basis of results of physical examination and laboratory tests. In general, in each age group there is an illness which occurs more frequently than in other age groups; however, it would be a false conclusion drawn from this fact that there exists no healthy individual.

It is believed that on the basis of the references provided it is obvious that those who require a continuous (therapeutic or preventive) folic acid treatment as in KAFRISSEN et al, or those who have diabetes as in SPELLACY et al, or have cervical dysplasia as in BUTTERWORTH et al, cannot be considered healthy. The NIH and FDA references discussed hereinabove unambiguously state that there exist healthy patients and that the term "healthy" cannot be considered indefinite.

The patients of KAFRISSEN et al have to take folic acid in any case, as they are afflicted with or predisposed to become afflicted with a disorder treatable by folic acid. The patients treated according to the presently claimed invention have to take folic acid only if they also must take a gestagen hormone; otherwise they should not take folic acid. Whether a patient falls

within the scope of the method of treatment disclosed in KAFRISSEN et al, within the scope of the presently claimed method of treatment, or within the scope of a third group, can be unambiguously decided on the basis of medical examination and laboratory tests.

Namely, on the basis of said medical examinations and laboratory tests, the patients are grouped into the following groups:

- patients with normal results fall within the scope of the patients treated according to the present invention;

- patients with abnormal results fall within the scope of the KAFRISSEN et al method if the abnormal results show that the individual is afflicted with or predisposed to become afflicted with a disorder treated by folic acid administration; and

- patients with abnormal results, wherein the abnormality is not connected to disorders treated by folic acid belong to a third group.

Thus in the Applicant's view it is not only that Applicant's patients treated according to the present method do not fall within the scope of KAFRISSEN et al, but furthermore there is even a third group of patients.

Applicant maintains that the SPELLACY et al reference provides no basis to reject claims 20, 28, 29, 31, 32, 33, 35, 37 and 39 now presented as either anticipated under 35 USC 102 or as obvious under 35 USC 103. The patients disclosed in SPELLACY et al are not the same healthy patients that are treated according to the

present invention and there is no suggestion in SPELLACY et al to treat the otherwise healthy patients according to the presently claimed method.

The patients of SPELLACY et al became diabetic in the course of the gestagen treatment. On the contrary, as it has been already detailed, the patients of the present invention are healthy - apart from the indication of the hormone therapy - at the beginning of the treatment and remain healthy in the course of the hormone treatment. Diabetes is not an indication of hormone treatment, therefore, the patients of Spellacy and those of the invention are separate.

SPELLACY et al suggests that diabetic patients take Vitamin B6 together with their contraceptive. According to the teaching of the present invention, non-diabetics also have to take Vitamin B6 together with the contraceptive.

SPELLACY et al does not teach that healthy patients also have to take Vitamin B6 together with the contraceptive, as in the tests disclosed therein the patients who were either already ill, or became ill (patient 10) had started hormone therapy already 3-6 months before they started to take also vitamins (page 267 line 7, page 267 paragraph 1). In other words, those who were treated with hormone+vitamin were ill patients.

Applicant also adds that while most of the patients who take contraceptive do not become diabetic as a result of the hormone treatment, in the case of SPELLACY et al, all of the patients became diabetic. This fact suggests that the patients of

SPELLACY et al were in fact predisposed to become diabetic even before the start of the treatment solely with the gestagen hormone (without Vitamin B6).

Applicant maintains that the BUTTERWORTH et al reference provides no basis to reject any of claims 20, 27, 32, 33, 34, 35 and 39 as anticipated under 35 USC 102 or as obvious under 35 USC 103. Reference is made to page 74, Materials and Methods, paragraph 1 of BUTTERWORTH et al according to which "Candidates for study were selected from a population of young women referred to a Public Health Colposcopy Clinic for evaluation of an abnormal cervical smear".

Accordingly, the patients of BUTTERWORTH et al had cervical dysplasia already at the beginning of the folic acid treatment, therefore, they were not healthy. In other words first they were treated solely with a gestagen hormone, due to which they have become afflicted with cervical dysplasia, and afterwards they started to take also folic acid.

According to the last sentence of the abstract, "...such a derangement [in folate metabolism] is an integral component of the dysplasic process that may be arrested (not prevented!) or in some cases reversed by oral folic acid supplementation." Accordingly, in contrast to the opinion of the Examiner, BUTTERWORTH et al does not suggest that healthy patients undertake folic acid treatment for prevention. This is further confirmed in the Discussion part (page 81, column 2, penultimate line of paragraph 1): "The present study findings suggest that until the

situation is further clarified an evaluation of nutritional status regarding folic acid would also be appropriate in patients with early cervical intraephitelial neoplasia."

The patients of BUTTERWORTH et al became afflicted with cervical dysplasia in the course of the hormone treatment. On the contrary, as it has been already detailed, the patients treated according to the presently claimed method are healthy - apart from the indication of the hormone therapy - at the beginning of the treatment and remain healthy in the course of the hormone treatment. Cervical dysplasia is not an indication of hormone treatment, therefore, the patients of BUTTERWORTH et al and those of the invention are separate, and so the reference is not anticipatory. Nor is there any suggestion in BUTTERWORTH et al to treat the otherwise healthy patients according to the present invention with both a gestagen hormone and folic acid.

The patients of BUTTERWORTH et al were administered 10 mg of folic acid (see the Abstract). The present inventor, however, suggested a maximum of 5 mg.

Applicant maintains that the combination of FERMO et al and JACKSON et al is in no way suggestive of the presently claimed method of treatment 9 through 12, 20, and 25 through 39. According to the Examiner, on the basis of the combination of FERMO et al and JACKSON et al the present invention is obvious. There is first of all no disclosure or suggestion in either FERMO et al or JACKSON et al to administer a gestagen hormone together with a plasma homocysteine reducing agent. Nor is there any connection disclosed

or suggested in either reference of any correlation between elevated plasma homocysteine levels and administration of a gestagen hormone. Nor is there any indication that administration of a plasma homocysteine reducing agent to an otherwise healthy patient receiving gestagen hormone therapy would prevent thromboembolism in the patient.

Applicant does not agree with the Examiner's conclusion of the obviousness of the present claims in view of these two references in combination and as support for the unobviousness of the present invention, Applicant is enclosing three documents in "Enclosure 2." Said documents disclose that hormones do not cause elevated homocysteine level. Therefore, a skilled person reading FERMO et al and JACKSON et al, either individually or in combination, would conclude that hormone treatment does not effect the homocysteine status of the patient. Thus, it is not suggested to take any homocysteine reducing agent in a hormone treatment.

As it has been argued before, JACKSON et al suggests the combination of vitamins and minerals for perimenopausal woman in order to prevent or reduce "life stage associated health risks". As taking gestagen hormones is not a life stage associated health risk, it is believed that this citation does not give any guidance to a skilled person to administer to a patient the present method of treatment of the present invention including both a gestagen hormone and a plasma homocysteine reducing agent.

In addition JACKSON et al suggests the administration of 400-440 µg of folic acid, the invention suggests 500 µg to 5 mg.

Applicant would like to draw the attention that, according to page 5, lines 19-26 of the specification, while the plasma homocysteine concentration is diminished by folic acid by 45-50% in hyperhomocysteinaemia of genetic origin (according to the state of the art), it is diminished by 69% in hyperhomocysteinaemia induced by hormones (according to the invention, see also Example c) on page 8, line 13). In biological systems this difference in the effectiveness of the treatments is considered as significant.

Lastly Applicant turns to the Examiner's refusal to accept the Declaration Under 37 CFR 1.131 that Applicant filed together with his previous amendment. Applicant filed the declaration to show that he conceived of the invention well before the effective date of KAFRISSEN et al as a reference under 35 USC 102e and then diligently reduced his invention to practice. By submitting the evidence of conception of his invention prior to the effective date of KAFRISSEN et al as a reference and diligent reduction of his invention to practice, Applicant has removed the Examiner's basis for maintaining a rejection of the claims under this section of the statute. Therefore 35 USC 102e should no longer be a basis to apply the KAFRISSEN et al reference against any claim in this application.

Applicant understands that the Examiner has maintained his rejection of claims 9, 11, 20, 27, 32 through 36 and 39 under 35 USC 102e in view of KAFRISSEN et al in view of MPEP 706.02(b)(D)(D) which essentially states that a Declaration Under 37 CFR 1.131 may not be used to antedate an issued US Patent or

published US Patent Application where the claims are directed to the same invention or to obvious variants thereof. The Examiner takes the position that the claims of KAFRISSEN et al either overlap with the Applicant's claims or are obvious variants of the Applicant's claims. Applicant disagrees.

Applicant believes that no claim now in the application should be rejected under 35 USC 102e in view of KAFRISSEN et al since the patient treated according to all of the present claims is a different patient from the patient treated according to KAFRISSEN et al. All of the patients treated according to KAFRISSEN et al are patients who are in need of folic acid treatment and so they are not healthy patients. There is no indication even in claims 9 and 11 now presented that the patients treated according to the present invention are not healthy patients. Applicant especially believes that claims 20, 27, 32 through 36 and 39, all directed to a method of reducing a risk in an otherwise healthy patient of thromboembolism induced by administration of a gestagen hormone by administering to the patient a therapeutically effective amount of a plasma homocysteine reducing agent, should not be rejected as anticipated by KAFRISSEN et al, and in fact believes that KAFRISSEN et al is not even an effective reference against these claims.

As explained hereinabove, the patient treated according to KAFRISSEN et al is not an "otherwise healthy patient" but is a patient whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher than normal incidence. Applicant has explained hereinabove why there is no overlap between

the patient defined in KAFRISSEN et al and the patient treated according to the presently claimed invention. Applicant has also explained why it would not be obvious from KAFRISSEN et al to treat the otherwise healthy patient according to the present invention to prevent a risk of thromboembolism according to claims 20, 27, 32 through 36 and 39. Therefore with regard to claims 20, 27, 32 through 36 and 39 there is no reason why the Declaration Under 37 CFR 1.131 should not be accepted and KAFRISSEN et al removed as an effective reference.

Favorable action in this case is earnestly solicited.

Respectfully submitted,
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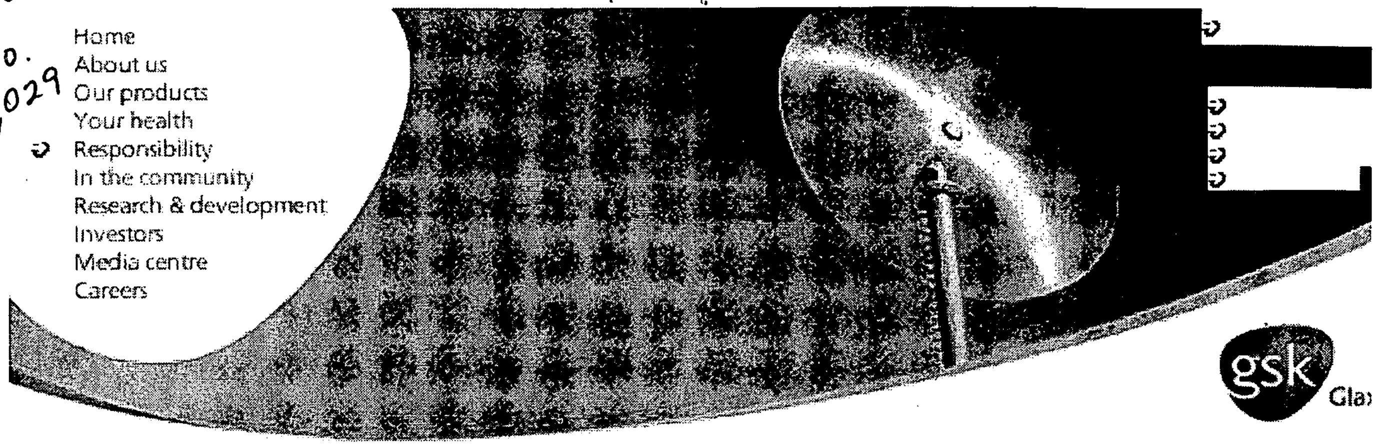
Enclosures: 10 Internet references defining "healthy patient"
Enclosure 1
Enclosure 2

21965
Ser. No. 09/890,029



Healthy volunteer studies

Before a pharmaceutical company can initiate the evaluation of a new medicinal compound in humans, it must first conduct extensive preclinical or laboratory research. This research typically involves years of experiments including animals and human cells. If this stage of testing is successful, a pharmaceutical company provides these data to regulatory authorities, requesting approval to begin evaluating the drug in humans. This evaluation is done through clinical trials and is conducted in three main phases. Each phase addresses different questions that determine if the drug can proceed to the next phase.

It is an ethical requirement that participants in clinical trials voluntarily decide to take part after having been provided with understandable information about the study. In most studies the participants will be patients with the disease or condition for which the new medicine is being evaluated. In the earliest phase of human trials (Phase I) when only the basic characteristics of the new medicine are being assessed, the volunteers normally do not have the disease or condition, ie they are healthy volunteers.

Phase I studies are primarily concerned with assessing the drug's safety in humans. An attempt is made to establish the dose range tolerated by volunteers for single and for multiple doses. These studies are designed to determine what happens to the drug in the human body - how it is absorbed, metabolised, and excreted. This initial phase of testing in humans is usually conducted in a small number of healthy volunteers (20 to 100), who are reimbursed for their time and discomfort and based on both the study design and the trends/practices for compensation in the local area. Sometimes these studies are conducted in patients (eg, cancer studies) and this may include research into how the disease may impact the way in which the drug is handled in the human body.

An Ethics Committee (EC) or Institutional Review Board (IRB) approval is required to ensure that appropriate safeguards are in place to protect the rights and welfare of research subjects.

This initial phase of testing typically takes several months. About 70 per cent of experimental drugs pass this initial phase of testing.

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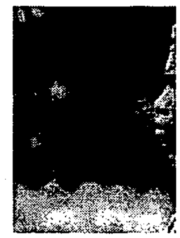

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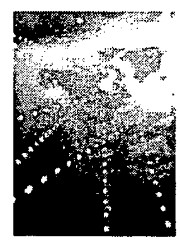

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Updated 30 January 2006

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Ser. No. 09/890,029

Adipex Phentermine
Diet Pills

Diet Pills Glossary of Weight Loss Terr

Adipex - A Brand Name for Phentermine, an appetite suppressant used reduce calorie intake.

Adipocytes - The scientific term for Fat Cells, being various typ specialized cells found in adipose tissue used for fat storage. One perhaps say this it is a rather obese term for Fat Cells. ;-)

Adipose - The fat found in Adipose tissue.

Adipose tissue - A specialized type of tissue for storing cellular fat.

Amino acids - The essential building blocks of Proteins, nine of cannot be manufactured by the body and therefor have to be obt through food intake.

Anorectic drugs - Pharmaceutical drugs designed as appetite suppres to reduce calorie intake.

Anorexia Nervosa - A psychophysiological disorder characterized l abnormal fear of becoming obese and therefor a distorted self-image results in an unwillingness to eat leading to severe weight loss. It car be accompanied by vomiting, excessive exercise and other physiol changes.

Bariatric - The branch of medicine dealing with the causes, preventior treatment of obesity, both pharmacological and surgical.

Binge Eating Disorder - An eating disorder involving uncontrolled eat large amounts of food but without vomiting or laxative purging.

Body Mass Index (BMI) - A calculation used by researchers physicians to estimate the ratio of your body weight to your height, th estimating the degree by which you are over or underweight and th the fat load on your body.

Bontril SR - An appetite suppressant that works by stimulating the ne system.

Bulimia Nervosa - An eating disorder involving episodic binge e followed by feelings of guilt, depression, and self-condemnation. It also involves measures to prevent weight gain, such as self-induced vom

American Heart Association

Food and Drug Administration

Nutrition and Health!

Phentermine Articles

Phentermine Fact List

Weight Control Information Network

BMI Calculator
Diet Pills Glossary
Mexican Pharmacy

excessive laxatives, dieting, or fasting.

Calories - A unit of measurement for the amount of energy that is rel from food upon oxidation by the body. Also the amount of heat requi raise the temperature of 1 kilogram of water by 1°C at 1 atmos pressure.

Carbohydrates - A group of organic compounds, including sugars, sta and fiber, that is a major source of energy for animals.

Cellulite - The dimples and bumps in the skin, usually around the t and buttocks, caused when the natural structure of the skin is stretch Fat cells growing too large.

Compulsive Overeating - Also known as Binge Eating.

Didrex - An appetite suppressant that works by stimulating the ne system.

Diet - The food and drink a person or animal consumes in their norma and a regulated eating plan for medical reasons or as a measure to prc weight loss.

Diuretics - A drug that increases the discharge of urine, used to move through the body quickly as a form of purging..

Exercise - A physical or mental activity used as a method of maintaini improving a level of fitness. An important part of an overall weight los: of action.

Fad Diets - Fashionable or Trendy diets that may or may not actuall in reducing weight. These diets should be used with caution a professional medical opinion sought.

Fastin - A brand name for Phentermine previously manufactured by : Kline Beecham but no longer available.

Fat - Animal tissue containing glycerol and fatty acids. Also used to de: someone who has too much fat and is therefor plump or obese.

FDA - The Food & Drug Administration is the US Federal agency respo for the regulation of biotechnology food products.

Generic Drug - A drug whose patent has expired thus enabling it manufactured by any company. Phentermine is an example of a G Drug.

Health - The overall condition of an organism at a given time in rega soundness of body or mind and freedom from disease or abnormality.

Meridia (sibutramine) - A weight loss diet pill that suppresses appet inhibiting the re-uptake of applicable hormones.

Metabolism - The chemical processes that take place within a living (organism that break down substances to provide energy and/or materials which are then re-synthesized into new and necessary subst to support life.

Nutraceutical - A naturally occurring food (Garlic, Soy) or food supple (Cod Liver Oil) believed to have beneficial effects on human health.

Nutritionist - An expert trained in the field of nutrition who is able advice in regard to allergies or health problems, and plan healthy di assist in weight loss.

Obese, Obesity - The condition having and increased body weight c by excessive accumulation of fat. This is usually indicated as having a Mass Index in excess of 30.

Overweight - The condition of weighing more than is normal or healtl one's age or build. This is usually indicated as having a Body Mass higher than 25 but lower than 30.

Phentermine - An appetite suppressant that disrupts the transmissi signals from the neurotransmitters and is used in the manageme obesity.

Proteins - A group of complex organic macromolecules that are the building blocks of all living cells and are therefore essential in the d animals for the growth and repair of tissue.

Saturated Fats - Fatty acids that are saturated with Hydrogen atom: mainly found in animal tissue, and should be restricted in the diet.

Simple Sugars - Single Molecule sugars such as glucose, fructose galactose.

Sucrose - A crystalline form of fructose and glucose found in many and extracted as ordinary table sugar.

Tenuate - An Appetite Suppressant that works by stimulating the c nervous system, increasing heart rate and blood pressure and decre your appetite.

Xenical (Orlistat) - A Diet Drug that works in the digestive syste blocking about one-third of the fat you eat from being digested.

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FAQs About Clinical Studies

If you are in the process of learning about clinical trials or are considering participating in one, you may be interested in looki Research (pdf) (Requires Adobe's free Acrobat Reader), which describes the role of a patient in clinical research. In addition anyone with questions to call the Patient Recruitment Office at **1-800-411-1222**. You may also want to try the "Topics A-Z" tc alphabetical index to all visitor- and patient-related subject areas.

1. **What are clinical studies?**

   Clinical studies are research studies in which real people participate as volunteers. Clinical research studies (sometir or protocols) are a means of developing new treatments and medications for diseases and conditions. There are stric clinical trials, which are monitored by the National Institutes of Health and the U.S. Food and Drug Administration. Sc research studies at the Clinical Center involve promising new treatments that may directly benefit patients.

2. **Why should I participate?**

   The health of millions has been improved because of advances in science and technology, and the willingness of thc individuals like you to take part in clinical research. The role of volunteer subjects as partners in clinical research is c quest for knowledge that will improve the health of future generations. Without your help, the research studies at the cannot be accomplished.

3. **What is a "healthy volunteer"?**

   A volunteer subject with no known significant health problems who participates in research to test a new drug, device is known as a "healthy volunteer" or "Clinical Research Volunteer." The clinical research volunteer may be a membei community, an NIH investigator or other employee, or family members of a patient volunteer. Research procedures v volunteers are designed to develop new knowledge, not to provide direct benefit to study participants. Clinical resear have always played a vital role in medical research. We need to study healthy volunteers for several reasons: When new technique such as a blood test or imaging device, we need clinical research volunteers to help us define the limi These volunteers are recruited to serve as controls for patient groups. They are often matched to patients on such cl age, gender, or family relationship. They are then given the same test, procedure, or drug the patient group receives. learn about the disease process by comparing the patient group to the clinical research volunteers.

4. **What are Phase I, Phase II and Phase III studies?**

   The phase 1 study is used to learn the "maximum tolerated dose" of a drug that does not produce unacceptable sid volunteers are followed primarily for side effects, and not for how the drug affects their disease. The first few voluntee receive low doses of the trial drug to see how the drug is tolerated and to learn how it acts in the body. The next grou subjects receives larger amounts. Phase 1 studies typically offer little or no benefit to the volunteer subjects.

   The phase 2 study involves a drug whose dose and side effects are well known. Many more volunteer subjects are side effects, learn how it is used in the body, and learn how it helps the condition under study. Some volunteer subje from a phase 2 study.

The phase 3 study compares the new drug against a commonly used drug. Some volunteer subjects will be given tl some the commonly used drug. The trial is designed to find where the new drug fits in managing a particular conditio the true benefit of a drug in a clinical trial is difficult. Determining the true benefit of a drug in a clinical trial is difficult.

5. **What is a placebo?**

Placebos are harmless, inactive substances made to look like the real medicine used in the clinical trial. Placebos all investigators to learn whether the medicine being given works better or no better than ordinary treatment. In many st successive time periods, with either the placebo or the real medicine. In order not to introduce bias, the patient, and staff, are not told when or what the changes are. If a placebo is part of a study, you will always be informed in the co to you before you agree to take part in the study. When you read the consent form, be sure that you understand wha approach is being used in the study you are entering.

6. **What is the placebo effect?**

Medical research is dogged by the *placebo effect* - the real or apparent improvement in a patient's condition due to w by the investigator or the patient. Medical techniques use three ways to rid clinical trials of this problem. These meth discredit some previously accepted treatments and validate new ones. Methods used are the following: randomizatio double-blind studies, and the use of a placebo.

7. **What is randomization?**

Randomization is when two or more alternative treatments are selected by chance, not by choice. The treatment cho the highest level of professional care and expertise, and the results of each treatment are compared. Analyses are d during a trial, which may last years. As soon as one treatment is found to be definitely superior, the trial is stopped. Ir fewest number of patients receive the less beneficial treatment.

8. **What are single-blind and double-blind studies?**

In single- or double-blind studies, the participants don't know which medicine is being used, and they can describe w without bias. Blind studies are designed to prevent anyone (doctors, nurses, or patients) from influencing the results. scientifically accurate conclusions. In single-blind ("single-masked") studies, only the patient is not told what is being double-blind study, only the pharmacist knows; the doctors, nurses, patients, and other health care staff are not infor medically necessary, however, it is always possible to find out what the patient is taking.

9. **Are there risks involved in participating in clinical research?**

Risks are involved in clinical research, as in routine medical care and activities of daily living. In thinking about the ris it is helpful to focus on two things: the degree of harm that could result from taking part in the study, and the chance occurring. Most clinical studies pose risks of minor discomfort, lasting only a short time. Some volunteer subjects, ho experience complications that require medical attention. The specific risks associated with any research protocol are detail in the consent document, which you are asked to sign before taking part in research. In addition, the major risk in a study will be explained to you by a member of the research team, who will answer your questions about the stud deciding to participate, you should carefully weigh these risks. Although you may not receive any direct benefit as a r participating in research, the knowledge developed may help others.

10. **What safeguards are there to protect participants in clinical research?**

The following section describes safeguards that protect the safety and rights of volunteer subjects. These safeguard

- **The Protocol Review Process**
- **Informed Consent Procedures**
- **The Patient Representative**
- **The Patient Bill of Rights**

Protocol review. As in any medical research facility, all new protocols produced at NIH must be approved by an inst board (IRB) before they can begin. The IRB, which consists of medical specialists, statisticians, nurses, social worke ethicists, is the advocate of the volunteer subject. The IRB will only approve protocols that address medically importa a scientific and responsible manner.

Informed consent. Your participation in any Clinical Center research protocol is voluntary. For every study in which participate, you will receive a document called "Consent to Participate in a Clinical Research Study" that explains the straightforward language. A member of the research team will discuss the protocol with you, explain its details, and a questions. Reading and understanding the protocol is your responsibility. You may discuss the protocol with family a will not be hurried into making a decision, and you will be asked to sign the document only after you understand the r protocol and agree to the commitment. At any time after signing the protocol, you are free to change your mind and c participate further. This means that you are free to withdraw from the study completely, or to refuse particular treatm Sometimes, however, this will make you ineligible to continue the study. If you are no longer eligible or no longer wis study, you will return to the care of the doctor who referred you to NIH.

Patient representative. The Patient Representative acts as a link between the patient and the hospital. The Patient makes every effort to assure that patients are informed of their rights and responsibilities, and that they understand w Center is, what it can offer, and how it operates. We realize that this setting is unique and may generate questions a role in the research process. As in any large and complex system, communication can be a problem and misunderst occur. If any patient has an unanswered question or feels there is a problem they would like to discuss, they can call Representative.

Bill of Rights. Finally, whether you are a clinical research or a patient volunteer subject, you are protected by the Cli Patients' Bill of Rights. This document is adapted from the one made by the American Hospital Association for use in the country. The bill of rights concerns the care you receive, privacy, confidentiality, and access to medical records.

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Phase 1 Clinical Studies

Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and may be conducted in patients, but are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies.

Phase 1 studies also evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans. These studies also determine which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects included in Phase 1 studies varies with the drug, but is generally in the range of twenty to eighty.

In Phase 1 studies, CDER can impose a clinical hold (i.e., prohibit the study from proceeding or stop a trial that has started) for reasons of safety, or because of a sponsor's failure to accurately disclose the risk of study to investigators. Although CDER routinely provides advice in such cases, investigators may choose to ignore any advice regarding the design of Phase 1 studies in areas other than patient safety.

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US FDA doc attachment
healthy volunteer

FAQs on GCP >>

Clinical Trial Management | Ethics Committee | Informed Consent | Serious Adverse Event

CLINICAL TRIAL MANAGEMENT

1 How do we select a central laboratory?

Central Laboratory Services are a paramount component of a clinical trial. Although there is no regulatory requirement for central laboratory, the requirements of ICH GCP (data quality, documentation of procedures and document control) mean that central laboratory facilities are useful as part of integrated clinical trial procedures.

The criteria for selecting central laboratory are:

- Adherence to Good Laboratory Practice (GLP)
- Accreditation by a reputed international organization e.g. College of American Pathologists (CAP)
- Accreditation in India by National Accreditation Board for Testing and Calibration Laboratories (NABL)
- Quality assurance
- Staff training
- Efficiency of processing samples
- Speed of services
- Networking and transport of samples
- Past track record/ experience in a clinical trial.

2 What is the role of Independent Data-Monitoring Committee (IDMC) in a trial?

As per the ICH-GCP guidelines, the definition of Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee) is as follows: An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify or stop a trial. US FDA has developed "Guidance for Clinical Trial Sponsors On the Establishment and Operation of Clinical Trial Data Monitoring Committees".

The increasing use of IDMCs in industry-sponsored trials is due to several factors, including:

- the growing number of industry-sponsored trials with mortality or major morbidity endpoints;
- the increasing collaboration between industry and government in sponsoring major clinical trials, resulting in industry trials performed under the policies of government funding agencies, which often require IDMCs;
- heightened awareness within the scientific community of problems in clinical trial conduct and

analysis that might lead to inaccurate and/ or biased results, especially when early termination for efficacy is a possibility, and demand for approaches to protect against such problems.

All clinical trials do not require monitoring by a formal committee external to the trial organizers and investigators. IDMCs have generally been established for large, randomized multi-site studies that evaluate interventions intended to prolong life or reduce risk of a major adverse health outcome such as a cardiovascular event or recurrence of cancer.

Because monitoring of accumulating results is almost always essential in such trials, IDMCs should be established for controlled trials with mortality or major morbidity as a primary or secondary endpoint.

They may also be helpful in settings where trial participants may be at elevated risk of such outcomes even if the study intervention addresses lesser outcomes such as relief of symptoms.

Although IDMCs may prove valuable in other settings as well, an IDMC is not needed or advised for every clinical study.

3 In a multi-centric and centrally randomized phase III trial, can a patient enrolled in one of the sites be transferred to another site in the middle of a trial realizing a clear cut geographical advantage for the patient? As far as treatment is concerned, patient can get similar treatment from other site. What are the implications from GCP angle? Is it a practice that referral centers transfer patients in the middle of a trial to the regional centers very often?

There are several implications, which are discussed below: Ethics Committee (EC) of the site where patient was first enrolled (site 1) is responsible for overseeing the safety of the patient. If the patient is transferred to another site (site 2) you will need to inform EC of site 1 about the transfer of the patient. The EC can ask the reasons for the transfer and you will need their written agreement/ approval for this action. You will also need approval of EC of site 2, as they will have to take responsibility of the transferred patient's safety. This process is likely to take quite sometime as EC usually meets as per their schedule.

This means that the patient has to continue the follow up visits at site 1 till both ECs have given their agreement/ approval. This will also apply to SAE reporting.

If this practice is to be followed for all patients with geographical advantage, you will have to amend the protocol & obtain EC and Regulatory approvals.

Drug accountability and Randomization: If the trial is centrally randomized, it would be difficult to manage randomization, drug supplies and drug accountability at site 1 and 2. Financial payment to investigators for the patient and source data verification at 2 sites will be other major issues. However, the most critical issue is viewpoint of auditors and Regulatory inspectors. There is an US FDA warning letter (Sep 27, 2000) issued to an investigator (Courtesy: Dr Tanuja Kulshreshtha Amdavad).

The relevant excerpt is given below:

Dr Jeffery R Levenson, MD. The Research Consortium Inc., 9303 Seminole Boulevard Florida.

Page 4 under "summary of violations related to requirements for investigator reporting to IRB (21 CFR 312.66)"

You did not report to IRB changes in the research activity and unanticipated problems involving risks to human subjects or others, and made changes in the research without IRB approval for example:

You did not obtain IRB approval for continuing study based activities at neighboring hospital or nursing homes (secondary institutions) to which subjects were transferred after their enrolment at the ——— for the

—— general hospital —. We note that you did not seek IRB approval for continuing research at secondary institution even after IRB specifically informed you that they could not continue to serve as the IRB to the second institution. Instead you incorrectly informed the IRB that secondary institutions were only providing "incidental care" and were not research sites, when in fact you were conducting research on subjects and collecting data at these institutions."

In view of the above issues, transfer of patients in middle of the trial from site 1 to 2 is unlikely to be a common practice. If geographical location is an issue, the patient should be referred to the Centre in other city before screening, as the address would be known at that time!

4 Can the Principal Investigator delegate the duty of measuring blood pressure and recording on the source notes to a study team member who is not a physician?

Yes. If he/ she can demonstrate and document, that the person who is given the task has received such a training. Nurses do take BP in intensive care units and hospitals. If BP is an end point for efficacy/ safety, it is advisable to delegate this function to a physician. Even for bioequivalence studies, some sponsors insist that a physician should measure pulse and BP.

5 If one were using the traditional method of randomization (based on randomization list generated by data management and not IVRS) and If there are two requests for randomization from the investigator almost at the same time (within a gap of 1 min), but the date of consent of the subjects to the trial are different and they have been found eligible after screening on the same day then how should one go about randomizing the subject?

Although the dates of consent are different, as the randomization is on the same day one would first randomize the patient, whose request came 1 min earlier.

6 During the audit, how do you select the sample number of case report forms (CRFs) for source data verification? How much time is required for an audit?

There does not appear to be a consistent approach to CRF selection within the industry as different methods are being used by the companies. Some use square root of number of CRFs plus one (usually using total number of enrolled subjects - this can either include or exclude screened subjects depending on the company). Some define a minimum range, for example 3-5 CRFs.

Some companies' do 100 per cent Source Data Verification (SDV) for consent forms and then 100 per cent of SDV for 10 per cent of total CRFs. At the time of report audit, all primary efficacy data and adverse events would be audited 100 per cent for all patients randomized and/ or enrolled. Some companies only allow one day for an audit for one auditor, and in this case it would be difficult to review more than three CRFs in adequate detail unless the study was very simple.

If there are particular problems then it might be necessary to extend the review to more CRFs, or if there are so many discrepancies on the first two CRFs that there is no point reviewing any more as the recommendation would be for someone to re-monitor all CRFs.

7 Is it necessary that the Investigator should be a clinician? Can a Para-clinical person become an investigator?

Indian GCP guidelines insist that the investigator should be a medical person. Indian GCP 3.3.1.

Qualifications: The investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the study and should have qualifications prescribed by the Medical Council of India (MCI).

ICH-GCP does not insist on a particular medical qualification.

ICH GCP 4.1 Investigator's Qualifications and Agreements. 4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority (ies).

In case of bio-equivalence study, US FDA guidance (Compliance Program Guidance Manual For FDA Staff Chapter 48 Bioresearch Monitoring Human Drugs In-Vivo Bio-equivalence Compliance Program 7348.00) is as follows:

The clinical investigator in a bio-equivalence study is involved in the screening and dosing of human subjects, and will ordinarily be a physician. Ph. D clinical pharmacologists and Pharm. Ds are acceptable if a physician is available to cover medical emergencies.

8 For the phase I clinical trial who should be considered as healthy volunteer? Or what is the definition of a healthy volunteer?

US FDA guidance on General Considerations for Clinical Evaluation of Drugs discussed this issue. The term healthy suggests that volunteer should be free from abnormalities which could complicate interpretation of the experiment or which might increase the sensitivity of the volunteer to the toxic potential of the drug. Healthy volunteer is one who has no evidence of any clinical, biochemical or investigational abnormality (based on physical examination, lab investigations (hematology, liver function, renal function, blood sugar, cholesterol, triglycerides) and x-ray chest, ECG.

9 Kindly let me know whether there are any particular recommendations for the list of laboratory tests, which are to be performed in pre-study investigations for the volunteers? What are the criteria for inclusion of particular tests in pre-study/ post-study laboratory investigations? Is there any correlation between the study drug and inclusion of pre-study laboratory tests, apart from testing the patient's well being (inclusion criteria)?

US FDA guidance for the industry, "General Considerations for the clinical evaluation of drugs" suggests the following investigations for phase I volunteers:

- CBC including platelet, urinalysis, BUN or creatinine, liver function, FBS or 2 hour postprandial sugar, ECG.
- Any other investigations as per the profile of the drug under investigation.

For example, for a study on anti-platelet drug, it would be desirable to check BT, CT, PT in the [illegible] The importance of these tests is two fold. Volunteers should be free from abnormalities which would complicate the interpretation of experiment or which might increase the sensitivity of the subject to the toxic potential of the drug.

10 What is the situation of insurance and compensation in clinical trials in India?

Both ICH-GCP and Indian GCP provide guidelines on the issue: The compensation for trial related injury and claims are the essential items of informed consent form.

ICH-GCP 4.8.10: Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(j) The compensation and/ or treatment available to the subject in the event of trial-related injury.

Indian GCP 2.4.3.2. Essential information for prospective research on subjects

viii. free treatment for research related injury by the investigator/ institution;

ix. Compensation of subjects for disability or death resulting from such injury;

As regards insurance, ICH-GCP insists only if it is a regulatory requirement.

ICH-GCP 5.8 Compensation to Subjects and Investigators 5.8.1: If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/ the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

In contrast to ICH-GCP, Indian GCP is more explicit

Indian GCP 2.3.1.12. Finance and insurance

d. Study subjects should be satisfactorily insured against any injury caused by the study

e. The liability of the involved parties (investigator, sponsor/ manufacturer, institution(s) etc) must be clearly agreed and stated before the start of the study.

Indian GCP 2.4.7 also insists on compensation for accidental injury (temporary or permanent disability and death) and makes it obligatory for sponsor to provide compensation or insurance coverage. At present, it is difficult for a sponsor to obtain an insurance cover from Indian insurance companies. However, some general insurance companies are considering this. In absence of the insurance coverage, the pharmacy companies provide for indemnity to the investigator/ institute and agree to take care of medical costs for any trial related injury.

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Impact of the EU Directive on Ethical Review & Phase 1 Studies

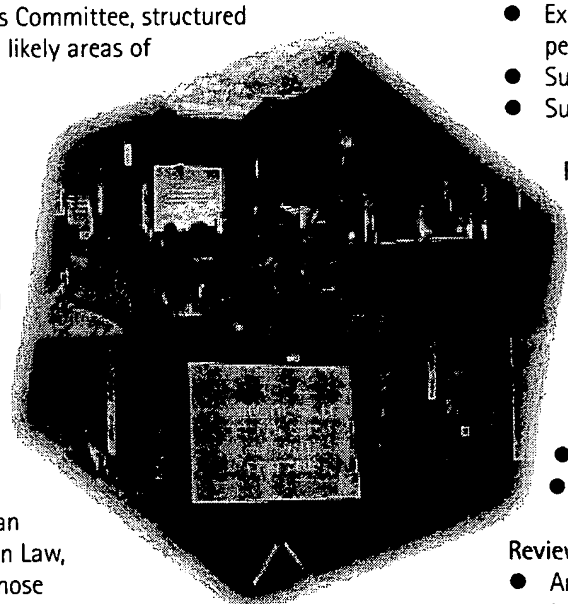
An Institute/ABPI Joint Seminar

Liz Allen, Annelies Legters, Angie Major, Lesley Shelford & Lisa Tan

This two-day seminar was the first meeting to be jointly organised by the Institute of Clinical Research and the ABPI. The meeting was designed to investigate the impact of the EU Clinical Trials Directive on Ethics and Phase 1 clinical trials. Around 130 delegates attended, coming from the pharmaceutical industry, CROs, Academia and NHS & Independent Ethics Committees.

On the first morning, there were two parallel sessions:

- A Seminar For New Members of Ethics Committees dealing with the role, responsibilities and issues facing a new member of an Ethics Committee, structured protocol review and likely areas of difficulty
- A Workshop for all other attendees discussing The Implications of the EU Clinical Trials Directive and GAFREC for Phase 1 Ethics Committees



Seminar for new members

Kathy Doyle, Barrister and Senior Lecturer at Manchester Metropolitan University specialising in Law, Medicine and Ethics, whose presentation was entitled 'Being a member of an Ethics Committee', described the background of ethical regulation of research involving humans, citing numerous examples from the Nuremberg Trials, the development of the 10 principles of the Nuremberg Code, and The Declaration of Helsinki. However, as ethical violations continued further regulation and guidance was issued by The Royal College of Physicians (1984), The ABPI (1988), and of course ICH (1996). Ethical violation continues today and we must all continue to be vigilant.

There are a number of issues to which members of an Ethics Committee (EC) must pay attention:

Relating to the protocol

- Objectives or purposes (are they worthwhile, reasonable, and ethical, and do they meet a clinical need?)
- Study design (is the design scientific, valid and able to meet the requirements of the objectives?)
- Statistical issues (are there sufficient subject numbers to enable meaningful interpretation of the data, and is the proposed analysis valid for the study design?)
- Experience of research staff who are to perform the study
- Suitability of facilities
- Sufficiency of resources

For studies involving volunteers

- Recruitment procedures (relationship with investigators and/or employers)
- Payment of volunteers (potential for financial inducement)
- Informed Consent procedures (extent and format of information provided, how consent is obtained, indemnity, and compensation)
- Confidentiality
- Requirements of regulatory authorities

Reviewing pre-clinical toxicology data

- Are there any findings that cause concern?
- Is there the need to consult an independent expert?
- Is sufficient information available to enable first administration into man?
- What are the potential adverse effects?
- Were there any serious unanticipated and unexplained effects in animals?

Dr Michael Goggin presented 'A Structured Review of a Protocol in Medical Research', highlighting the major sections of a protocol (e.g. title, purpose, design, procedures, etc.) and the

issues to be considered within those sections. Ideally, protocols should be clear and unambiguous detailing accurately the objectives, design, variables to be measured, and analysis of the data. The protocol should be well thought through and reviewers must be satisfied that the protocol is acceptable in its present form. If it is not acceptable then it must be revised. In addition, to enable reviewers to adequately review a protocol, Dr Goggin suggested use of a protocol checklist to ensure that all the issues listed above had been considered.

Next on the agenda, Dr Chris Pick gave a short presentation to introduce delegates to the field of toxicology. Unfortunately, the authors were unable to attend this session.

Dr Frank Wells presented "Some Likely Areas of Difficulty", describing problems in the recruitment of healthy volunteers taking into account potential safeguards against over-exposure, levels of payment (which should be appropriate but should not be at such a level to be considered coercion), the issues of using healthy female volunteers, and the issues of supervision of the volunteers during a study.

Screening of healthy volunteers is essential, but can generate some unexpected findings. Screening usually includes:

- Full medical history and physical examination
- Standard clinical and laboratory tests (electrocardiogram, HIV and hepatitis B screening, and screening for concealed therapeutic and recreational drugs)

A study by Singh and Williams[1] reported that between 1990-1994 of 1,293 volunteers screened 141 were rejected for medical reasons indicating that 10.9% of those screened were not healthy.

The safety of volunteers during a study is paramount. A survey by Orme et al[2] of medical conditions occurring in healthy volunteer studies involving the administration of medicines reported that 8,163 healthy volunteers participated in Phase 1 studies during 1986-1987. Of these 6.9% experienced minor adverse events, 0.5% experienced moderate adverse events and 0.04% experienced potentially life-threatening events.

GAFREC workshop for other attendees

Dr Richard Tiner, Medical Director of the APBI, reviewed the EU Clinical Trial Directive & Governance Arrangements For Research Ethics Committees (GAFREC) to highlight what independent Phase 1 ECs must do in order to comply with the Directive. The Directive states that Member States must take measures necessary for the establishment and operation of Research Ethics Committees (RECs), including governance for Independent Ethics Committees. Member States have until 1st May 2003 to prepare national provisions for complying with the Directive and must adopt these provisions by 1st May 2004. GAFREC is expected to be in place by April 2003, and will cover such aspects as:

- The role of the Research Ethics Committee
- The remit of an NHS REC
- Establishment and support of NHS RECs
- Membership requirements and process
- Composition of a REC
- Working procedures
- Multi-centre research
- The process of ethical review of a research protocol
- Submitting an application

Key points included of this presentation included:

- Independent RECs will be required to show that they are free from bias
- Appointment of members shall be by an open process
- An appointed member must be prepared to publish his/her full name, profession and affiliation
- Summary of details of the REC application shall be made publicly available once the final decision is ratified by the REC
- Annual reports are to be submitted to the appointing Authority

Effect of the EU-CTD on Ethics Committees

The afternoon session commenced with a presentation from Professor Terry Stacey, Director of Central Office of Research Ethics Committees (COREC) on 'The effect of the EU Clinical Trial Directive on Ethics Committees'. A new UK Ethics Committee Authority (UKECA) will be established. UKECA will be headed by the Ministers of Health for England, Scotland, Wales and Northern Ireland. The management structures for each country will differ, but UKECA will be the overall authority. UKECA will recognise MRECs, LRECs, universities, and independent ethics committees, all of whom will have to be accredited by UKECA in order to carry out the function and responsibilities of an Ethics Committee. Accreditation will ensure that the standards and processes of ECs are of the highest quality for ethical review, and the requirements of The Directive will ensure homogeneity throughout Europe. This accreditation will be in place by February 2004, and all existing ECs will be accredited by this date. As part of the

accreditation procedure, ECs must have a written constitution and SOPs, be able to demonstrate quality of ethical review, and have in place a training program for members.

It is currently proposed that ECs will be comprised of 18 members, one of whom will be the Chairman. A third of the membership will be 'lay members'. Members will not be allowed to serve for more than five years, and must be able to demonstrate that they have no financial interest in the business of the committee. It is anticipated that deputies will be allowed, and others can be co-opted on as members provided it can be demonstrated that they are appropriately trained. There will be an open process for recruitment of new members.

It is proposed that a quorum will be at least seven members, which must include the Chair, Vice Chair and a lay member. This group will review the primary protocol, protocol amendments and make the decision to grant ethical approval, refer or reject. It is anticipated that a subcommittee will consist of three members rather than two. A meeting can be held by telephone, providing that the meeting is scheduled and minuted.

RECs will need to produce Annual Reports for which guidance will be available. Discrete office facilities and administration together with appropriate finances and support for RECs will be a legal requirement.

The revised Green Book
Dr Michael Goggin gave a comprehensive review of the 'Green Book' – the second edition of the introduction to the work of RECs. This provides a guide to being a member on an REC considering human pharmacology (Phase 1) studies. All conference delegates were provided with a copy of the 'green book' published by the ABPI, which was released for publication that day!

Parallel workshops
Parallel workshops on "Recruitment, Inducement & Over volunteering" and "A Difficult Protocol" concluded the meeting's first day. Unfortunately, none of the authors attended the session on "A Difficult Protocol".

Dr Malcolm Boyce presented the Recruitment, Inducement & Over-Volunteering workshop. A survey of healthy volunteers recruited by Phase 1 units was presented in which a total of 6,000 healthy volunteers were involved, 68 of which were thought to have over-volunteered. Interestingly, 58 were men and only 10 were women; this amounts to a ratio of 1:100. A demonstration of the proposed TOPS program[3] was provided. TOPS stands for The Over-volunteering Prevention System, which will be used by eight UK Phase 1 Units. The purpose of this program is to identify 'over-volunteers' and has been designed to be quick and easy to use via the Internet. The Association of Independent Clinical Research Contractors[4] (AICRC) will take over hosting the register. The delegates also took part in a volunteer payment exercise.

The Impact of the EU Directive on Phase 1

The second day of the seminar focussed on the Impact of the EU Directive on Phase 1 clinical trials, and was relevant for anybody working in this field. Delegates included those from industry, Phase 1 units and academia. The morning was devoted to an update from the Medicines Controls Agency (MCA) and the perspective on all of this from an Investigator.

MCA perspective
Dr. Elaine Godfrey, Pharmaceutical Assessor with the Medicines Controls Agency (MCA), gave an overview of the Directive 2001/20/EC (CTD) and issues relating to Phase 1 studies. Detailed below are significant issues covered by Dr Godfrey.

The definition of a clinical trial is "any investigation in human subjects..." meaning that healthy volunteer studies will be subject to the same regulatory review as patient studies. This is obviously a significant change in the UK, where volunteer studies were not previously regulated. The MCA recognises this, including the significant increase in their workload that will result. They are committed to ensuring that the UK still remains a competitive place to perform Phase 1 studies and as such have addressed some key issues:

- The MCA has committed to assessing Phase 1 study applications in a mean time of 14 and a maximum of 21 days as opposed to the 60-day timeframe referenced in the CTD – this was received with enthusiasm.
- The European Commission Guidance Note on submissions to the Competent Authority will be expanded to include a section specifically on Phase 1 studies; this was also welcomed by attendees. A draft copy of this document will be circulated to other Competent Authorities for review. It was not clear whether wider review would be sought.
- The MCA are compiling training packages for both Phase 1 and non-commercial studies. As these are still in the planning stages, they stated that they would welcome external input.

A question was raised regarding the definition of a Phase 1 study by the MCA - Dr Godfrey

confirmed that current thinking included only healthy volunteer studies and special patient populations (e.g. studies in renally and hepatically impaired patients). However, it was raised by delegates that there are examples of Phase 1 studies in patients designed to show a physiological effect, which could not be of therapeutic benefit to those patients involved, and that these have not previously required approval. Dr Godfrey asked that details of such studies be provided via the ABPI for the MCA to consider further...

Dr Godfrey told delegates that the MCA Clinical Trials Unit is planning to implement a Phase 1 pilot. This is likely to take place in mid-2003, and it will cost £600 for pharmaceutical companies to volunteer to take part. (More details of this are available on AHPPI website[5]).

Next, Dr Godfrey noted that the definition of an Investigational Medicinal Product (IMP) is any active substance or placebo, and therefore includes comparators and placebo; as such, GMP will apply them too. Handling of IMPs will be reviewed by GCP auditors as part of an audit of a Phase 1 facility.

Another significant issue included in her presentation was the 'loss of the DDX', which will have significant implications for a number of people represented at the meeting as there is no longer a different process for investigator initiated studies.

Finally, picking up on the theme of the first day, Dr Godfrey reminded us again that the Directive provides a statutory basis for Ethics committees and GCP, once transcribed into UK law. This will also apply to independent IECs linked to Phase 1 units. The Directive also includes requirements for safety reporting.

Mr Ian Oulsnam, MCA GCP inspector went on to give an overview of the issues relating to inspection of Phase 1 clinical units and findings from recent audits. Mr Oulsnam also pointed out that the Directive introduces new powers in the UK:

- Power to inspect any site involved with a clinical trial in the UK.
- Power to levy fees for the conduct of an inspection - MCA currently charge £5000.

An overview of a typical GCP inspection of a Phase 1 unit was provided. He stated that the 'independence' of ethics committees would be assessed for units who use independent committees. Additionally, IMP handling and validation, etc. of all bespoke computer systems would be included in an audit

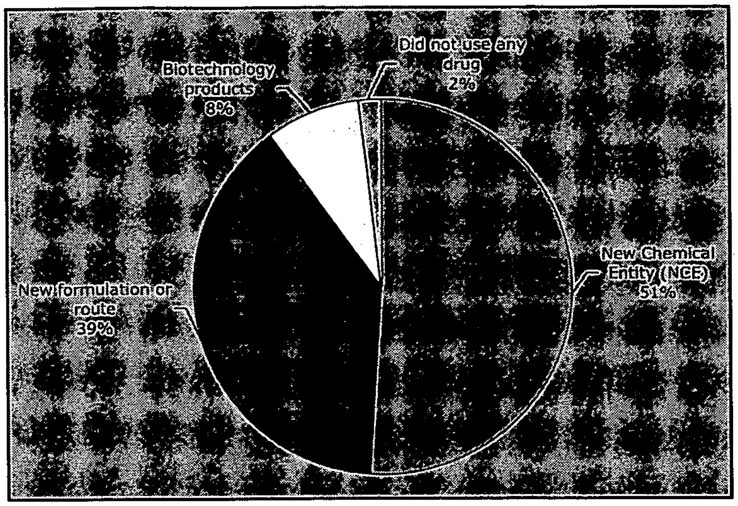
The main findings were then presented from the MCA voluntary inspections that have been performed to date. These include:

- Volunteer medical history/eligibility information not received from GPs
- Significant protocol amendments implemented prior to EC approval or following Chairman's action
- Inadequate procedures for nursing/physician cover out of normal working hours
- Inadequate procedures/facilities for the preparation of IMPs
- Inadequate procedures for unblinding blinded subjects in an emergency
- Inadequacies relating to contracts/agreements with sponsors, agencies and contractors
- Lack of recall procedures for emergency medication, support medication and comparator drugs
- Inadequate training of agency staff

Finally, Mr Oulsnam told delegates that consultation is underway prior to introduction of the new UK statutory instrument relating to mandatory inspections. A number of people have been asked to be involved in the process and the Institute will be asked to provide representation on behalf of our members.

The Investigator perspective

Dr. Steve Warrington's presentation considered the impact of the Directive from the viewpoint of an investigator at a Phase 1 unit. In order to give the audience an idea of the studies performed in a unit, he presented an analysis of over 300 studies performed at his unit between 1993 and 2001, and described the types of studies performed (see below):



Dr Warrington's impression was that a significant impact of the CTD would be the time taken to gain approval from the Competent Authority. He was reassured by the MCA's commitment to a 14-day review period for the original submission; however, he highlighted that an area of particular concern was the approval of protocol amendments. This relates to the requirement to submit all 'substantial amendments' to the Competent Authority prior to their implementation (Article 10a). A number of points were made around the definition of 'substantial', as this is not clearly defined in the Article.

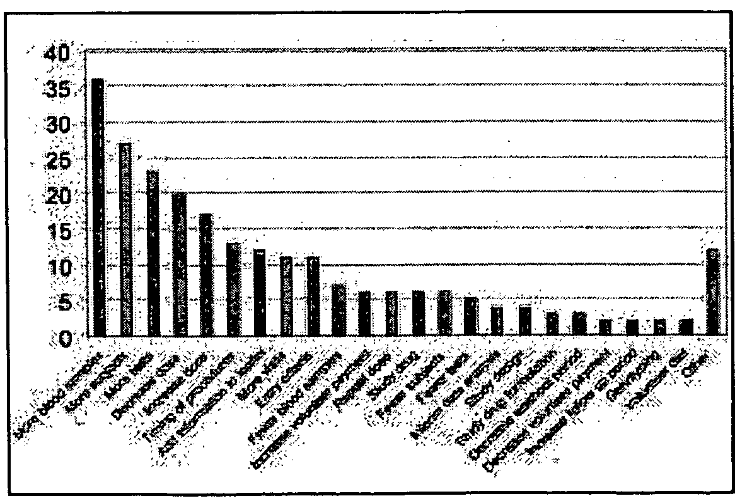
In order to describe his concerns, he presented data on the number and type of amendments produced for 280 studies. 143 amendments were given expedited review by the REC and these regularly included additional measurements, etc. (see opposite):

Under the current definition, many of these amendments would be considered 'substantial'. These amendments are often produced in Phase 1 studies based on emerging data and usually need to be implemented for the next dose in a study, which can be as little as 7 days later. The mean approval time for these amendments by Dr Warrington's local REC was 4 days and this is representative of the majority of Phase 1 units. This rapid review and approval is essential to ensure that the most appropriate data is obtained; it could be argued that it would be unethical to continue as before if the data collected is not the providing the most informed data to guide the early development programme. He suggested that in order to avoid this time-consuming step, sponsors may consider producing all-embracing protocols and he provided an example. In addition, he also provided examples of 'ultra-flexible protocols' for example a protocol might state 'extra assessments of BP, pulse rate and ECGs may be included depending on emerging data' or 'a dose range between Xmg and Ymg will be explored', rather than documenting actual doses to be studied.

Dr Warrington concluded by presenting some data from an AHPPI survey showing that >600 studies and >100 protocol amendments per year will be submitted for review. The majority of amendments will require expedited review and he stated that if Phase 1 units in the UK are to remain competitive, the response time from the MCA must match the current ethics committee timelines. He also stated that a definition of 'substantial amendments' for submission to the MCA is urgently needed.

Academic research

Dr Sally Burtles, Director of Drug Development for Cancer Research UK provided a very interesting presentation on the perceived impact of the CTD on academic and investigator-led studies. Cancer Research UK is the largest UK charity and provides the major funding of cancer research in the UK. They have an extensive trials portfolio focussing on early stage development of novel treatments and Phase 3 trials of licensed products. Therefore, Dr Burtles was well placed to provide this overview.



Dr Burtles highlighted three major areas of the Directive that will impact on academic clinical research:

- All clinical trials have to be undertaken to GCP standards

- All clinical trials supplies have to be made to Good Manufacturing Practice (GMP) standards in a licensed facility
- The loss of the DDX

She stated that, whilst the academic community can comply with all of these requirements in principle, the major barriers are costs (which will increase significantly) and the lack of relevant expertise within the academic community.

The requirement for GCP compliance is a major issue. Although Cancer Research UK's early clinical trials are undertaken to ICH GCP standards, the vast majority of academic clinical trials are not. Many studies do not have a single defined sponsor, with multiple individuals and agencies taking on different responsibilities. Most clinical groups can operate to GCP, as they do so when they undertake trials with companies; however, they probably do not have the documentation, systems or staff to operate to GCP themselves. GCP covers all aspects of a clinical trial, including the laboratory activities (PK and PD) and functional imaging assessments. The majority of academic labs do not have any quality systems in place, and a great deal of work and commitment will be needed in order to achieve acceptable standards by May 2004.

Dr Burtles also highlighted that getting novel agents developed to enable them to be made to GMP will increase the cost by 3-4x over the 'GMP-like' standards that are currently utilised by Cancer Research UK. For other academics who currently manufacture their own supplies (e.g. antibodies), they will no longer be able to do this and to contract production out will increase costs by an order of magnitude. Costs to contract out production are already very high, but there are insufficient licensed production facilities, which will allow the costs to increase further as demand outstrips supply. In addition to the cost, the academic community generally lacks the expertise required for understanding the issues around GMP production and release of materials for human use. A further related issue is the need for a Qualified Person (QP) to release the supplies for use, as the majority of academic investigator sites do not have this expertise available.

It is expected that the loss of the DDX will have a major impact on academic clinical research, particularly in the development of novel agents to be tested in Phase 1 and 2 trials. The proposed application procedure will require an extensive application with supporting data. There are concerns around the application that include having the expertise to write the dossier, and the

potential increase in costs to undertake more extensive pre-clinical studies.

Dr Burtles estimated that the cost of taking a new agent from academic research into Phase 1 clinical trials could increase by about 3 to 4 fold under the requirements of the Directive and GCP. She concluded that the Directive will have a major impact on all of us and we need to minimise the negative impact on academic clinical trials so that we can continue to provide data that will help improve the treatments available to cancer patients worldwide.

GMP/IMP issues

Mr Alan Newbery went over several Articles of the Directive, but concentrated on the issue of GMP requirements for IMP, including the necessary GMP procedures investigational sites will need to have in place.

He quoted some background information: the Directive refers to Directive 65/65/EEC and 75/318/EEC and the Declaration of Helsinki. He stated that 19 paragraphs and 23 articles cover everything from payments to minors (Art. 4) through to changes to scientific progress to GMP requirements (Art. 13 & 15). There is a clear definition for a clinical trial and also an IMP. An IMP is also defined in Article 2. Annex 13 of GMP, which is still a draft, covers the manufacture of investigational medicinal products. It covers issues such as quality management, personnel, premises and equipment, documentation requirements, manufacturing processes and their validation and packaging and labelling.

Under the new Directive the release of IMP for use in a clinical trial must be performed by a Qualified Person (QP), a European qualification only. The QP must ensure that the IMP has been manufactured in accordance with the requirements of European GMP. If an IMP is sourced from outside the EU the QP must also ensure the IMP has been manufactured in accordance with European GMP and the EU-CTD. Sourcing of IMPs outside of the EU may present a number of problems for QP release in order to satisfy the requirements of the Directive.

Pharmaceutical Industry Competitiveness Task Force

Dr. Richard Tiner gave the last presentation of the day on the Pharmaceutical Industry Competitiveness Task Force (PICTF). PICTF was established during a meeting at No.10 between the Prime Minister, Sir Richard Sykes and Sir Tom McKillop. Dr Tiner said that the UK is an expensive

place to do research but the quality of this research is good. He stated that 40% of clinical research is conducted by sponsor companies. At the initial meeting, the remit of PICTF was agreed and an action plan devised. This included:

1. Improve start up times from April 2001
2. DOH Research Governance Framework
3. Partnership agreement
4. Transparency in costing
5. Agreed performance indicators

The PICTF Clinical Research Group highlighted a need for a partnership between Industry and the NHS. The Research Partnership Agreement is PICTF's first completed action. A copy of this is available from the ABPI and Department of Health websites. The ABPI policy on registration of clinical trials has been prepared and should go live shortly. PICTF have worked with the MCA to ensure that the review timeframe for a CTX does not increase and this has been achieved; additionally they are working together to ensure that the percentage of CTX's granted within 36 days does not fall.

Costs and overheads have been investigated and there is increasing transparency within Trusts. It appears that some companies have historically been charged for participants' standard care during a clinical trial, whereas only treatment outside standard care should be charged for. Dr Tiner said that some NHS/Universities had been 'double-costing', and that the MRC were also unsure of what the costs were for.

To save time and money in setting up studies, a Model Clinical Trials Agreement has been written and is currently being reviewed by lawyers. The Agreement is a template for a contract between an NHS Trust and a sponsor. It is hoped that Sponsor companies and NHS Trusts will use this to ensure a timely and prompt start up of clinical trials in England. This should also promote consistency around the costs of a clinical trial.

Ongoing activities include the COREC novel processes review and the Good Publication Policy (available in Spring 2003). Data protection issues are also under review, as 15% of international studies have UK patients. Feasibility studies are currently being conducted to understand the issues. Clinical Research Networks are also being encouraged, with the Cancer Research Network as a good example already in existence. Other networks to be set up include mental health and paediatrics.

A benchmarking exercise is underway with 20 companies providing data. This exercise will be used to understand whether the implementation of the recommendations is ensuring that the UK remains at the forefront of clinical research. Early results show that the time for REC review is decreasing. However, 10-20% of REC applications are not valid as the application is not complete when submitted.

Dr Tiner was also asked to provide insight on the status of the implementation of the Directive outside the UK. He informed the participants that the situation outside the UK is not clear. However, current information suggests that the process in The Netherlands will not change significantly and the role of the Competent Authority will be performed by the CCMO (a central 'ethics committee') for most products. Currently the CCMO only deals with 'special products' such as gene therapy. The submission to Competent Authority is likely to take the form of a 'mini Common Technical Document' but this has not yet been finalised. There are some perceived difficulties in Germany, but the Scandinavian countries are moving forward in an efficient manner. However, the status in the Eastern Block is unknown. He concluded by stating that there isn't much information available on the implementation of the Directive in other counties and EFPIA are trying to build a database.

A short summary of the implications for RECs, as covered on the first day of this 2-day seminar, was the closing item of a very useful and interesting seminar, the first organised by the ABPI and the Institute of Clinical Research Phase 1-Sub-Committee.

Liz Allen is Director of Scientific Affairs, GDRU Quntiles Ltd, and Vice-Chair of the Phase 1 Sub-Committee, Annalies Legters is International Clinical Trial Coordinator, Lundbeck BV, Angie Major is Membership Development Manager, Institute of Clinical Research, Lesley Shelford is Senior CRA, Janssen-Cilag Ltd, and Lisa Tan is Clinical Project Scientist, Pfizer and Chair of the Phase 1 Sub-Committee, Annalies and Lesley are also members of the Phase 1 Sub-Committee.

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2 Orme, M, et al (1989): "Healthy volunteer studies in Great Britain: The results of a survey into 12 months activity in this field", Br. J Clin. Pharmacol. 27(2), p125-33.

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The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 26 July 2001
CPMP/EWP/QWP/1401/98

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON THE INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

DISCUSSION IN THE JOINT EFFICACY AND QUALITY WORKING GROUP	December 1997 – October 1998
TRANSMISSION TO CPMP	July 1998
RELEASE FOR CONSULTATION	December 1998
DEADLINE FOR COMMENTS	June 1999
DISCUSSION IN THE DRAFTING GROUP	February – May 2000
TRANSMISSION TO CPMP	July – December 2000
RELEASE FOR CONSULTATION	December 2000
DEADLINE FOR COMMENTS	March 2001
DISCUSSION IN THE DRAFTING GROUP	March - May 2001
TRANSMISSION TO CPMP	July 2001
ADOPTION BY CPMP	July 2001
DATE FOR COMING INTO OPERATION	January 2002

Note:

This revised Note for Guidance will replace the previous guideline adopted in December 1991.

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NOTE FOR GUIDANCE ON INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

TABLE OF CONTENTS

1 INTRODUCTION

To exert an optimal therapeutic action an active moiety should be delivered to its site of action in an effective concentration for the desired period. To allow reliable prediction of the therapeutic effect the performance of the dosage form containing the active substance should be well characterised.

In the past, several therapeutic misadventures related to differences in bioavailability (e.g. digoxin, phenytoin, primidone) testify to the necessity of testing the performance of dosage forms in delivering the active substance to the systemic circulation and thereby to the site of action. Thus the bioavailability of an active substance from a pharmaceutical product should be known and reproducible. This is especially the case if one product containing one certain active substance is to be used instead of its innovator product. In that case the product should show the same therapeutic effect in the clinical situation. It is generally cumbersome to assess this by clinical studies.

Comparison of therapeutic performances of two medicinal products containing the same active substance is a critical means of assessing the possibility of alternative use between the innovator and any essentially similar medicinal product. Assuming that in the same subject an essentially similar plasma concentration time course will result in essentially similar concentrations at the site of action and thus in an essentially similar effect, pharmacokinetic data instead of therapeutic results may be used to establish equivalence: bioequivalence.

It is the objective of this guidance to define, for products with a systemic effect, when bioavailability or bioequivalence studies are necessary and to formulate requirements for their design, conduct, and evaluation. The possibility of using *in vitro* instead of *in vivo* studies with pharmacokinetic end points is also envisaged.

This guideline should be read in conjunction with Directive 75-318/EEC, as amended, and other pertinent elements outlined in current and future EU and ICH guidelines and regulations especially those on:

- Pharmacokinetic Studies in Man
- Modified Release Oral and Transdermal Dosage Forms: Section I (Pharmacokinetic and Clinical Evaluation)
- Modified Release Oral and Transdermal Dosage Forms: Section II (Quality)
- Investigation of Chiral Active Substances.
- Fixed Combination Medicinal Products
- Clinical Requirements for Locally Applied, Locally Acting Products Containing Known Constituents.
- The Investigation of Drug Interactions
- Development Pharmaceutics
- Process Validation
- Manufacture of the Finished Dosage Form
- Validation of analytical procedures: Definitions and Terminology (ICH topic Q2A)
- Validation of analytical procedures: Methodology (ICH topic Q2B)
- Structure and Content of Clinical Study Reports (ICH topic E3)
- Good Clinical Practice: Consolidated Guideline (ICH topic E6)
- General Considerations for Clinical Trials (ICH topic E8)
- Statistical Principles for Clinical Trials (ICH topic E9)
- Choice of Control Group in Clinical Trials (ICH topic E10)
- Amendments to Commission Regulation on (EC) 542/95
- Common Technical Document (ICH topic M4)

For medicinal products not intended to be delivered into the general circulation the common

systemic bioavailability approach cannot be applied. Under these conditions the (local) availability may be assessed, where necessary, by measurements quantitatively reflecting the presence of the active substance at the site of action using methods specially chosen for that combination of active substance and localisation (see section 5.1.8). In this case, as well as in others, alternative methods may be required such as studies using pharmacodynamic end points. Furthermore, where specific requirements for different types of products are needed, the appropriate exceptions are mentioned therein.

This Note for Guidance does not explicitly apply to biological products.

2 DEFINITIONS

Before defining bioavailability and related terminology some definitions pertaining to dosage and chemical forms are given:

2.1 Pharmaceutical equivalence

Medicinal products are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards.

Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to faster or slower dissolution and/or absorption.

2.2 Pharmaceutical alternatives

Medicinal products are pharmaceutical alternatives if they contain the same active moiety but differ in chemical form (salt, ester, etc.) of that moiety or in the dosage form or strength.

2.3 Bioavailability

Bioavailability means the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action.

In the majority of cases substances are intended to exhibit a systemic therapeutic effect, and a more practical definition can then be given, taking into consideration that the substance in the general circulation is in exchange with the substance at the site of action:

> -Bioavailability is understood to be the extent and the rate at which a substance or its active moiety is delivered from a pharmaceutical form and becomes available in the general circulation.

It may be useful to distinguish between the "absolute bioavailability" of a given dosage form as compared with that (100%) following intravenous administration (e.g. oral solution *vs.* iv.), and the "relative bioavailability" as compared with another form administered by the same or another non intravenous route (e.g. tablets vs. oral solution).

2.4 Bioequivalence

Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.

Alternatively to classical bioavailability studies using pharmacokinetic end points to assess bioequivalence, other types of studies can be envisaged, e.g. human studies with clinical or pharmacodynamic end points, studies using animal models or in vitro studies as long as they are appropriately justified and/or validated.

2.5 Essentially similar products

The current EU definition for essentially similar products is as follows (see "The rules governing medicinal products in the European Union", Notice to Applicants, Vol. 2A in accordance with the December 1998 European Court of Justice ruling in the "Generics" case):

"A medicinal product is essentially similar to an original product where it satisfies the criteria of having the same qualitative and quantitative composition in terms of active substances, of having the same pharmaceutical form, and of being bioequivalent unless it is apparent in the light of scientific knowledge that it differs from the original product as regards safety and efficacy".

By extension, it is generally considered that for immediate release products the concept of essential similarity also applies to different oral forms (tablets and capsules) with the same active substance.

The need for a comparative bioavailability study to demonstrate bioequivalence is identified under 5.1. Concerns about differences in essentially similar medicinal products lie on the use of different excipients and methods of manufacture that ultimately might have an influence on safety and efficacy. A bioequivalence study is the widely accepted means of demonstrating that these differences have no impact on the performance of the formulation with respect to rate and extent of absorption, in the case of immediate release dosage forms. It is desirable that excipients must be devoid of any effect or their safe use is ensured by appropriate warning in the package label – see guideline on excipients in the label and package leaflet: "The Rules Governing Medicinal Products in the European Union", 1998, Vol. 3B, - and not interfere with either the release or the absorption process.

An essentially similar product can be used instead of its innovator product. An 'innovator' product is a medicinal product authorised and marketed on the basis of a full dossier i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. A 'Reference Product' must be an 'innovator' product (see 3.5).

2.6 Therapeutic equivalence

A medicinal product is therapeutically equivalent with another product if it contains the same active substance or therapeutic moiety and, clinically, shows the same efficacy and safety as that product, whose efficacy and safety has been established.

In practice, demonstration of bioequivalence is generally the most appropriate method of substantiating therapeutic equivalence between medicinal products, which are pharmaceutically equivalent or pharmaceutical alternatives, provided they contain excipients generally recognised as not having an influence on safety and efficacy and comply with labelling requirements with respect to excipients. (see 2.5).

However, in some cases where similar extent of absorption but different rates of absorption are observed the products can still be judged therapeutically equivalent if those differences are not of therapeutic relevance. A clinical study to prove that differences in absorption rate are not therapeutically relevant will probably be necessary.

3 DESIGN AND CONDUCT OF STUDIES

In the following sections, requirements for the design and conduct of bioavailability or bioequivalence studies are formulated. It is assumed that the applicant is familiar with pharmacokinetic theories underlying bioavailability studies. The design should be based on a reasonable knowledge of the pharmacodynamics and/or the pharmacokinetics of the active substance in question. For the pharmacokinetic basis of these studies reference is made to the recommendation "Pharmacokinetic studies in man". The design and conduct of the study

should follow EU-regulations on Good Clinical Practice, including reference to an Ethics Committee.

A bioequivalence study is basically a comparative bioavailability study designed to establish equivalence between test and reference products. The following sections apply mainly to bioequivalence studies. Since bioavailability studies are comparative in nature, the contents of the following sections apply to these studies as well, with the necessary adaptations in accordance with the aim of each specific study. Where necessary, specific guidance concerning bioavailability studies will be given.

The methodology of bioequivalence studies can be used to assess differences in the pharmacokinetic parameters in pharmacokinetic studies such as drug-drug or food-drug interactions or to assess differences in subsets of the population. In this case the relevant guidelines should be followed and the selection of subjects, the design and the statistical analysis should be adjusted accordingly.

3.1 Design

The study should be designed in such a way that the formulation effect can be distinguished from other effects. If the number of formulations to be compared is two, a two-period, two-sequence crossover design is often considered to be the design of choice.

However, under certain circumstances and provided the study design and the statistical analyses are scientifically sound alternative well-established designs could be considered such as parallel design for very long half-life substances and replicate designs for substances with highly variable disposition.

In general, single dose studies will suffice, but there are situations in which steady-state studies

- may be required, e.g. in the case of
  - dose- or time-dependent pharmacokinetics,
  - some modified release products (in addition to single dose investigations),
- or can be considered, e.g.
  - if problems of sensitivity preclude sufficiently precise plasma concentration measurements after single dose administration.
  - if the intra-individual variability in the plasma concentration or disposition precludes the possibility of demonstrating bioequivalence in a reasonably sized single dose study and this variability is reduced at steady state.

In such steady-state studies the administration scheme should follow the usual dosage recommendations.

The number of subjects required is determined by

a) the error variance associated with the primary characteristic to be studied as estimated from a pilot experiment, from previous studies or from published data,

b) the significance level desired,

c) the expected deviation from the reference product compatible with bioequivalence (delta) and

d) the required power.

The clinical and analytical standards imposed may also influence the statistically determined number of subjects. However, generally the minimum number of subjects should be not smaller than 12 unless justified.

Subsequent treatments should be separated by adequate wash out periods. In steady-state studies wash out of the previous treatment last dose can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least three times the terminal half-life).

The sampling schedule should be planned to provide an adequate estimation of C_{max} and to cover the plasma concentration time curve long enough to provide a reliable estimate of the extent of absorption. This is generally achieved if the AUC derived from measurements is at least 80% of the AUC extrapolated to infinity. If a reliable estimate of terminal half-life is necessary, it should be obtained by collecting at least three to four samples during the terminal log linear phase.

In order to study bioavailability under steady-state conditions when differences between morning and evening or nightly dosing are known, (e.g. if it is known that the circadian rhythm is known to have an influence on bioavailability), sampling should be carried out over a full 24 hours cycle.

For drugs with a long half-life, relative bioavailability can be adequately estimated using truncated AUC as long as the total collection period is justified. In this case the sample collection time should be adequate to ensure comparison of the absorption process.

3.2 Subjects

3.2.1 Selection of subjects

The subject population for bioequivalence studies should be selected with the aim to minimise variability and permit detection of differences between pharmaceutical products. Therefore, the studies should normally be performed with healthy volunteers. The inclusion/exclusion criteria should be clearly stated in the protocol.

Subjects could belong to either sex; however, the risk to women of childbearing potential should be considered on an individual basis.

In general, subjects should be between 18 - 55 years old and of weight within the normal range according to accepted normal values for the Body Mass Index. They should be screened for suitability by means of clinical laboratory tests, an extensive review of medical history, and a comprehensive medical examination. Depending on the drug's therapeutic class and safety profile special medical investigations may have to be carried out before, during and after the completion of the study. Subjects should preferably be non-smokers and without a history of alcohol or drug abuse. If moderate smokers are included (less than 10 cigarettes per day) they should be identified as such and the consequences for the study results should be discussed.

3.2.2 Standardisation of the study

The test conditions should be standardised in order to minimise the variability of all factors involved except that of the products being tested. Therefore, standardisation of the diet, fluid intake and exercise is recommended. Subjects should preferably be fasting at least during the night prior to administration of the products. If the Summary of Product Characteristics of the reference product contains specific recommendations in relation with food intake related to food interaction effects the study should be designed accordingly.

The time of day for ingestion should be specified and as fluid intake may profoundly influence gastric passage for oral administration forms, the volume of fluid (at least 150 ml) should be constant. All meals and fluids taken after the treatment should also be standardised in regard to composition and time of administration during the sampling period. The subjects should not take other medicines during a suitable period before and during the study and should abstain from food and drinks, which may interact with circulatory, gastrointestinal,

liver or renal function (e.g. alcoholic or xanthine-containing beverages or certain fruit juices). As the bioavailability of an active moiety from a dosage form could be dependent upon gastrointestinal transit times and regional blood flows, posture and physical activity may need to be standardised.

3.2.3 Inclusion of patients

If the investigated active substance is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy volunteers it may be necessary to use patients instead, under suitable precautions and supervision. In this case the applicant should justify the alternative.

3.2.4 Genetic phenotyping

Phenotyping and/or genotyping of subjects should be considered for exploratory bioavailability studies and all studies using parallel group design. It may be considered as well in crossover studies (e.g. bioequivalence, dose proportionality, food interaction studies etc.) for safety or pharmacokinetic reasons. If a drug is known to be subject to major genetic polymorphism, studies could be performed in panels of subjects of known phenotype or genotype for the polymorphism in question.

3.3 Characteristics to be investigated

In most cases evaluation of bioavailability and bioequivalence will be based upon the measured concentrations of the parent compound. In some situations, however, measurements of an active or inactive metabolite may be necessary instead of the parent compound. Such situations include cases where the use of a metabolite may be advantageous to determine the extent of drug input, e.g. if the concentration of the active substance is too low to be accurately measured in the biological matrix (e.g. major difficulty in analytical method, product unstable in the biological matrix or half-life of the parent compound too short) thus giving rise to significant variability.

Bioequivalence determinations based on metabolites should be justified in each case bearing in mind that the aim of a bioequivalence study is intended to compare the *in vivo* performance of test and reference products. In particular if metabolites significantly contribute to the net activity of an active substance and the pharmacokinetic system is non-linear, it is necessary to measure both parent drug and active metabolite plasma concentrations and evaluate them separately.

In bioavailability studies, the shape of and the area under the plasma concentration *versus* time curves are mostly used to assess extent and rate of absorption. The use of urine excretion data may be advantageous in determining the extent of drug input in case of products predominately excreted renally, but has to be justified when used to estimate the rate of absorption. Sampling points or periods should be chosen, such that the time- concentration profile is adequately defined so as to allow the estimation of relevant parameters.

From the primary results, the bioavailability characteristics desired are estimated, namely AUC_t, AUC_∞, C_{max}, t_{max}, Ae_t, Ae_∞ as appropriate, or any other justifiable characteristics (cf. Appendix I). The method of estimating AUC-values should be specified. For additional information $t_{1/2}$ and MRT can be estimated. For studies in steady state AUC_τ, C_{max}, C_{min} and fluctuation should be provided.

In bioequivalence studies the AUC_t is the most reliable reflection of the extent of absorption.

The exclusive use of compartmental based estimates are not recommended.

If pharmacodynamic effects are used as characteristics the measurements should provide a sufficiently detailed time course, the initial values in each period should be comparable and the complete effect curve should remain below the maximum physiological response.

Specificity, accuracy and reproducibility of the methods should be sufficient. The non-linear character of the dose/response relationship should be taken into account and base line corrections should be considered during data analysis.

3.4 Chemical analysis

The bioanalytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice (GLP).

The bioanalytical methods used to determine the active moiety and/or its biotransformation product(s) in plasma, serum, blood or urine or any other suitable matrix must be well characterised, fully validated and documented to yield reliable results that can be satisfactorily interpreted. The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of an analyte(s) concentration in a specific biological matrix. The characteristics of a bioanalytical method essential to ensure the acceptability of the performance and the reliability of analytical results are: (1) stability of the stock solutions and of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage; (2) specificity; (3) accuracy; (4) precision (5) limit of quantification and (6) response function.

The validation of a bioanalytical method should comprise two distinct phases: (1) the pre-study phase in which the compliance of the assay with the six characteristics listed above is verified and (2) the study phase itself in which the validated bioanalytical method is applied to the actual analysis of samples from the biostudy mainly in order to confirm the stability, accuracy and precision.

A calibration curve should be generated for each analyte in each analytical run and it should be used to calculate the concentration of the analyte in the unknown samples in the run. A number of separately prepared Quality Control samples should be analysed with processed test samples at intervals based on the total number of samples. In addition, it is necessary to validate the method of processing and handling the biological samples.

All procedures should be performed according to pre-established Standard Operating Procedures (SOPs). All relevant procedures and formulae used to validate the bioanalytical method should be submitted and discussed. Any modification of the bioanalytical method before and during analysis of study specimens may require adequate revalidation; all modifications should be reported and the scope of revalidation justified.

According to the requirements of the note for guidance on the "Investigation of Chiral Active Substances", bioequivalence studies supporting applications for essentially similar medicinal products containing chiral active substances should be based upon enantiomeric bio-analytical methods unless (1) both products contain the same stable single enantiomer; (2) both products contain the racemate and both enantiomers show linear pharmacokinetics.

3.5 Reference and test product

Test products in an application for a generic product are normally compared with the corresponding dosage form of an innovator (see 2.5) medicinal product (reference product). The choice of reference product should be justified by the applicant.

For an abridged application claiming essential similarity to a reference product, application to numerous Member States based on bioequivalence with a reference product from one Member State can be made.

Such an application can be considered acceptable unless there is a significant difference between the reference products originating from the same manufacturer (or its subsidiaries/licensees), in terms of the qualitative and quantitative composition in excipients. Concerned Member States may request information from the first Member State on the

reference product, namely on the composition, manufacturing process and finished product specification.

Where additional bioequivalence studies are required, they should be carried out using the product registered in the concerned Member State as the reference product

It should be remembered that the development of the test product should always take into account the Note for Guidance on "Development Pharmaceutics".

The test products used in the biostudy must be prepared in accordance with GMP-regulations. Batch control results of the test product should be reported.

In the case of oral solid forms for systemic action the test product should usually originate from a batch of at least 1/10 of production scale or 100 000 units, whichever is greater, unless otherwise justified. The production of batches used should provide a high level of assurance that the product and process will be feasible on an industrial scale; in case of production batch smaller than 100 000 units, a full production batch will be required. If the product is subjected to further scale-up this should be properly validated.

Samples of the product from full production batches should be compared with those of the test batch, and should show similar in vitro dissolution profiles when employing suitable dissolution test conditions (see Appendix II).

The study sponsor will have to retain a sufficient number of all investigational product samples in the study for one year in excess of the accepted shelf life or two years after completion of the trial or until approval whichever is longer to allow re-testing, if it is requested by the authorities.

In accordance with Annex 13 to the EU guide to GMP, reference and test product must be packed in an individual way for each subject included in the bioequivalence trial. Every effort should be made to allow a precise tracking of administration of the reference and test products to the subjects, for instance by the use of labels with a tear-off portion.

3.6 Data analysis

The primary concern of bioequivalence assessment is to quantify the difference in bioavailability between the reference and test products and to demonstrate that any clinically important difference is unlikely.

3.6.1 Statistical analysis

The statistical method for testing relative bioavailability (e.g. bioequivalence) is based upon the 90% confidence interval for the ratio of the population means (Test/Reference), for the parameters under consideration.

This method is equivalent to the corresponding two one-sided test procedure with the null hypothesis of bioinequivalence at the 5% significance level. The statistical analysis (e.g. ANOVA) should take into account sources of variation that can be reasonably assumed to have an effect on the response variable. A statistically significant sequence effect should be handled appropriately.

Pharmacokinetic parameters derived from measures of concentration, e.g. AUC, C_{max} should be analysed using ANOVA. The data should be transformed prior to analysis using a logarithmic transformation.

If appropiate to the evaluation the analysis technique for t_{max} should be non-parametric and should be applied to untransformed data. For all pharmacokinetic parameters of interest in addition to the appropriate 90% confidence intervals for the comparison of the two formulations, summary statistics such as median, minimum and maximum should be given.

3.6.2 Acceptance range for pharmacokinetic parameters

The pharmacokinetic parameters to be tested, the procedure for testing and the acceptance ranges should be stated beforehand in the protocol.

In studies to determine average bioequivalence the acceptance intervals for the main characteristics are detailed as follows:

AUC-ratio

The 90% confidence interval for this measure of relative bioavailability should lie within an acceptance interval of 0.80-1.25. In specific cases of a narrow therapeutic range the acceptance interval may need to be tightened.

In rare cases a wider acceptance range may be acceptable if it is based on sound clinical justification.

C_{max}-ratio

The 90% confidence interval for this measure of relative bioavailability should lie within an acceptance interval of 0.80-1.25. In specific cases of a narrow therapeutic range the acceptance interval may need to be tightened.

In certain cases a wider interval may be acceptable. The interval must be prospectively defined e.g. 0.75-1.33 and justified addressing in particular any safety or efficacy concerns for patients switched between formulations.

Others

Statistical evaluation of t_{max} only makes sense if there is a clinically relevant claim for rapid release or action or signs related to adverse effects. The non-parametric 90% confidence interval for this measure of relative bioavailability should lie within a clinically determined range.

For other (see 3.3) pharmacokinetic parameters in comparison relative bioavailability (e.g. C_{min}, Fluctuation, $t_{1/2}$, etc.) considerations analogous to those for AUC, C_{max} or t_{max} apply, taking into consideration the use of log-transformed or untransformed data, respectively.

3.6.3 Handling deviations from the study plan

The method of analysis should be planned in the protocol. The protocol should also specify methods for handling drop-outs and for identifying biologically implausible outliers. Post hoc exclusion of outliers is generally not accepted. If modelling assumptions made in the protocol (e.g. for extrapolating AUC to infinity) turn out to be invalid, a revised analysis in addition to the planned analysis (if this is feasible) should be presented and discussed.

3.6.4 A remark on individual and population bioequivalence

To date, most bioequivalence studies are designed to evaluate average bioequivalence. Experience with population and individual bioequivalence studies is limited. Therefore, no specific recommendation is given on this matter.

3.7 In vitro dissolution complementary to a bioequivalence study

The results of "in vitro" dissolution tests, obtained with the batches of test and reference products that were used in the bioequivalence study should be reported. The results should be reported as profiles of percent of labelled amount dissolved versus time.

The specifications for the *in vitro* dissolution of the product should be derived from the dissolution profile of the batch that was found to be bioequivalent to the reference product and would be expected to be similar to those of the reference product (see Appendix II).

For immediate release products, if the dissolution profile of the test product is dissimilar

compared to that of the reference product and the in vivo data remain acceptable the dissolution test method should be re-evaluated and optimised. In case that no discriminatory test method can be developed which reflects in vivo bioequivalence a different dissolution specification for the test product could be set.

3.8 Reporting of results

The report of a bioavailability or a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with GCP-rules and related EU and ICH E3 guidelines. This implies that the authenticity of the whole of the report is attested by the signature of the principal investigator. The responsible investigator(s), if any, should sign for their respective sections of the report.

Names and affiliations of the responsible investigator (s), site of the study and period of its execution should be stated. The names and batch numbers of the products used in the study as well as the composition(s), finished product specifications and comparative dissolution profiles should be provided. In addition, the applicant should submit a signed statement confirming that the test product is the same as the one that is submitted for marketing authorisation.

All results should be clearly presented and should include data from subjects who eventually dropped-out. Drop-out and withdrawal of subjects should be fully documented and accounted for. The method used to derive the pharmacokinetic parameters from the raw data should be specified. The data used to estimate AUC should be reported. If pharmacokinetic models are used to evaluate the parameters the model and computing procedure used should be justified. Deletion of data should be justified.

All individual subject data should be given and individual plasma concentration/time curves presented in linear/linear and log/linear scale. The analytical report should include the results for all standard and quality control samples as well. A representative number of chromatograms or other raw data should be included covering the whole concentration range for all, standard and quality control samples as well as the specimens analysed. The analytical validation report should be submitted as well.

The statistical report should be sufficiently detailed to enable the statistical analysis to be repeated, e.g. randomisation scheme, demographic data, values of pharmacokinetic parameters for each subject, descriptive statistics for each formulation and period. A detailed ANOVA and/or non-parametric analysis, the point estimates and corresponding confidence intervals including the method of their estimation should also be included.

4 APPLICATIONS FOR PRODUCTS CONTAINING NEW ACTIVE SUBSTANCES

4.1 Bioavailability

In the case of new active substances (new chemical entities) intended for systemic action, the pharmacokinetic characterisation will have to include the determination of the systemic availability of the substance in its intended pharmaceutical form in comparison with intravenous administration. If this is not possible (e.g. not technically feasible or for safety reasons) the bioavailability relative to a suitable oral solution or suspension should be determined. In the case of a prodrug the intravenous reference solution should preferably be made of the active moiety.

4.2 Bioequivalence

During development bioequivalence studies are necessary as bridging studies between (i) pivotal and early clinical trial formulations; (ii) pivotal clinical trial formulations, especially those used in the dose finding studies, and the to-be-marketed medicinal product; (iii) other

comparisons depending on the situation. Such studies may be exempted if the absence of differences in the in vivo performance can be justified by satisfactory in vitro data (see 5.1.1 and 5.2).

5 APPLICATIONS FOR PRODUCTS CONTAINING APPROVED ACTIVE SUBSTANCES

5.1 Bioequivalence studies

In vivo bioequivalence studies are needed when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence.

The kind of studies to be performed may vary with the type of product, as follows.

5.1.1 Oral Immediate Release Forms with Systemic Action

This section pertains to dosage forms such as tablets, capsules and oral suspensions and takes into consideration criteria derived from the concepts underlying the Biopharmaceutics Classification System, i.e. high solubility, high permeability for the active substance and high dissolution rate for the medicinal product. These criteria, along with a non-critical therapeutic range should be primarily considered; therefore the following characteristics have to be taken into account in order to justify the request for exemption from in vivo bioequivalence studies. Hence data must be supplied to justify the absence of such studies.

a) Characteristics related to the active substance:

i - risk of therapeutic failure or adverse drug reactions:

this risk depends on the requirements of special precautions with respect to precision and accuracy of dosing of the active substance, e.g. the need for critical plasma concentrations;

ii - risk of bioinequivalence:

evidence of bioavailability problems or bioinequivalence exists for some specific active substances;

iii – solubility:

When the active substance is highly water soluble, the product could be in general exempted from bioquivalence studies unless, considering the other characteristics, the exemption could entail a potential risk. Polymorphism and particle size are major determinants of dissolution rate and special attention should be paid to these characteristics. An active substance is considered highly water soluble if the amount contained in the highest dose strength of an immediate release product is dissolved in 250 ml of each of three buffers within the range of pH 1-8 at 37°C (preferably at or about pH 1.0, 4.6, 6.8);

iv - pharmacokinetic properties:

linear and complete absorption indicating high permeability reduces the possibility of an immediate release dosage form influencing the bioavailability.

b) Characteristics related to the medicinal product:

i - rapid dissolution

in case of exemption from bioequivalence studies, in vitro data should demonstrate the similarity of dissolution profile between the test product and the reference product in each of three buffers within the range of pH 1-8 at 37°C (preferably at or about pH 1.0, 4.6, 6.8). However, in cases where more than 85% of the active substance are dissolved within 15 minutes, the similarity of dissolution

profiles may be accepted as demonstrated (see appendix II);

ii – <u>excipients</u>

the excipients included in the composition of the medicinal product are well established and no interaction with the pharmacokinetics of the active substance is expected. In case of atypically large amounts of known excipients or new excipients being used, additional documentation has to be submitted;

iii – <u>manufacture</u>

the method of manufacture of the finished product in relation with critical physicochemical properties of the active substance (e.g. particle size, polymorphism) should be adequately addressed and documented in the development pharmaceutics section of the dossier.

5.1.2 Oral solutions

If the product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an oral solution currently approved as a medicinal product, no bioequivalence study is required, provided the excipients contained in it do not affect gastrointestinal transit, absorption or in vivo stability of the active substance.

In those cases where an oral solution has to be tested against an oral immediate release formulation a comparative bioavailability study will be required unless an exemption can be justified (see 5. 1. 1).

5.1.3 Non-Oral Immediate Release forms with systemic action

In general bioequivalence studies are required.

5.1.4 Modified Release and transdermal dosage forms

Requirements for bioequivalence studies in accordance with the specific guideline

5.1.5 Fixed combinations products

Combination products should in general be assessed with respect to bioavailability and bioequivalence of individual active substances either separately (in the case of a new combination) or as an existing combination. Criteria under 5.1.1 will apply to individual components. The study in case of a new combination should be designed in such a way that the possibility of a pharmacokinetic drug-drug interaction could be detected.

5.1.6 Parenteral solutions

The applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised product.

In the case of other parenteral routes, e.g. intramuscular or subcutaneous, if the product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same or comparable excipients as the medicinal product currently approved, then bioequivalence testing is not required.

5.1.7 Gases

If the product is a gas for inhalation a bioequivalence study is not required.

5.1.8 Locally applied products

a) Locally acting

For products for local use (after oral, nasal, inhalation, ocular, dermal, rectal, vaginal etc. administration) intended to act without systemic absorption the approach to determine

bioequivalence based on systemic measurements is not applicable and pharmacodynamic or comparative clinical studies are in principle required. The lack of them should be justified (see specific Note for Guidance).

Whenever systemic exposure resulting from locally applied, locally acting medicinal products entails a risk of systemic adverse reactions, systemic exposure should be measured.

b) Systemically acting

For locally applied products with systemic action a bioequivalence study is always required.

5.2 In Vitro Dissolution

Dissolution studies are always necessary and consequently required. . In vitro dissolution testing forms a part of the assessment of a bioequivalence waiver request based on criteria as described in section 5.1. Dissolution studies must follow the guidance as laid out in Appendix II.

5.3 Variations

If a product has been reformulated from the formulation initially approved or the manufacturing method has been modified by the manufacturer in ways that could be considered to impact on the bioavailability, a bioequivalence study is required, unless otherwise justified. Any justification presented should be based upon general considerations, e.g. as per 5.1.1, or on whether an acceptable in vivo / in vitro correlation has been established.

In cases where the bioavailability of the product undergoing change has been investigated and an acceptable correlation between in vivo performance and in vitro dissolution has been established, the requirements for in vivo demonstration of bioequivalence can be waived if the dissolution rate in vitro of the new product is similar to that of the already approved medicinal product under the same test conditions as used to establish the correlation (see Appendix II)

In all other cases bioequivalence studies have to be performed.

For variations of the innovator product the reference product for use in bioequivalence and dissolution studies is usually that authorised under the current formula, manufacturing method, packaging etc. and the product manufactured in line with the proposed changes is tested against this.

When variations to an essentially similar product are made the reference product for the bioequivalence study should be the innovator product.

5.4 Dose proportionality in immediate release oral dosage forms

If a new application concerns several strengths of the active substance a bioequivalence study investigating only one strength may be acceptable. However the choice of the strength used should be justified on analytical, pharmacokinetic and safety grounds. Furthermore <u>all</u> of the following conditions should be fulfilled:

- the pharmaceutical products are manufactured by the same manufacturer and process;
- the drug input has been shown to be linear over the therapeutic dose range (if this is not the case the strengths where the sensitivity is largest to identify differences in the two products should be used);
- the qualitative composition of the different strengths is the same;
- the ratio between amounts of active substance and excipients is the same, or, in the case of preparations containing a low concentration of the active substance (less than 5%), the ratio between the amounts of excipients is similar;

- the dissolution profile should be similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

If a new strength (within the approved dose range) is applied for on the basis of an already approved medicinal product and all of the stated conditions hold then a bioequivalence study is not necessary.

5.5 Suprabioavailability

If suprabioavailability is found, i.e. if the new product displays an extent of absorption appreciably larger than the approved product, reformulation to a lower dosage strength should be considered. In this case, the biopharmaceutical development should be reported and a final comparative bioavailability study of the reformulated new product with the old approved product should be submitted.

In case reformulation is not carried out the dosage recommendations for the suprabioavailable product will have to be supported by clinical studies. Such a pharmaceutical product should not be accepted as therapeutically equivalent to the existing reference product. If marketing authorisation is obtained, the new product may be considered as a new medicinal product.

To avoid confusion for both prescribers and patients, it is recommended that the name of suprabioavailable product precludes confusion with the older approved product

Suprabioavailable products cannot claim "essential similarity" (see section 2.5) with the innovator product.

APPENDIX I

Explanation of the symbols in paragraph 3.3

C_{max}:	maximal plasma concentration;
C_{min}:	minimal plasma concentration;
C_{av}:	average plasma concentration;
t_{max}:	time passed since administration at which the plasma concentration maximum occurs;
AUC_t:	area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_∞:	area under the plasma concentration curve extrapolated to infinite time;
AUC_τ:	AUC during a dosage interval in steady state;
MRT:	mean residence time;
Ae_t:	cumulative urinary excretion from administration until time t;
Ae_∞:	cumulative urinary excretion extrapolated to infinite time;
$t_{1/2}$:	plasma concentration half-life;
Fluctuation:	$(C_{max} - C_{min})/C_{av}$
Swing:	$(C_{max} - C_{min})/C_{min}$

APPENDIX II

Dissolution testing

A medicinal product is composed of drug substance and excipients and the proportion between them, the type of excipients and the manufacturing method of the final product are chosen based on the content, the physicochemical and the bulk properties of the drug and on its absorption properties. Taken as a whole this gives each product certain dissolution characteristics.

During the development of a medicinal product a dissolution test is used as a tool to identify formulation factors that are influencing and may have a crucial effect on the bioavailability of the drug. As soon as the composition and the manufacturing process are defined a dissolution test is used in the quality control of scale-up and of production batches to ensure both batch-to-batch consistency and that the dissolution profiles remain similar to those of pivotal clinical trial batches. Furthermore, a dissolution test can be used to support the bioavailability of a new drug product, the bioequivalence of an essentially similar product or variations.

Therefore, dissolution studies can serve several purposes:

i - Quality assurance

- To get information on the test batches used in bioavailability/bioequivalence studies and pivotal clinical studies to support specifications for quality control.
- To be used as a tool in quality control to demonstrate consistency in manufacture
- To get information on the reference product used in bioavailability/bioequivalence studies and pivotal clinical studies

ii -Bioequivalence surrogate inference

- To demonstrate similarity between reference products from different Member States
- To demonstrate similarity between different formulations of an active substance (variations and new, essentially similar products included) and the reference medicinal product
- To collect information on batch to batch consistency of the products (test and reference) to be used as basis for the selection of appropriate batches for the in vivo study.

The test methodology should be in accordance with pharmacopoeial requirements unless those requirements are shown to be unsatisfactory. Alternative methods can be considered when justified that these are discriminatory and able to differentiate between batches with acceptable and non-acceptable performance of the product in vivo.

If an active substance is considered highly soluble, it is reasonable to expect that it will not cause any bioavailability problems if, in addition, the dosage system is rapidly dissolved in the physiological pH-interval expected after product administration. A bioequivalence study may in those situations be waived based on case history and similarity of dissolution profiles which are based on discriminatory testing, provided that the other exemption criteria in 5.1.1 are met. The similarity should be justified by dissolution profiles, covering at least three time points, attained at three different buffers (normally pH range 1-6.8; in cases where it is considered necessary pH range 1-8).

In the case of a drug or excipients that are insensitive to pH, profiles from only two buffer systems are required.

If an active substance is considered to have a low solubility and a high permeability, the rate limiting step for absorption may be dosage form dissolution. This is also the case when one or more of the excipients are controlling the release and subsequent dissolution step of the active

substance. In those cases a variety of test conditions is recommended and adequate sampling should be performed until either 90% of the drug is dissolved or an asymptote is reached. Knowledge of dissolution properties under different conditions e.g. pH, agitation, ionic strength, surfactants, viscosity, osmotic pressure is important since the behaviour of the solid system in vivo may be critical for the drug dissolution independent of the physico-chemical properties of the active substance. An appropriate experimental statistical design may be used to investigate the critical parameters and for the optimisation of such conditions.

Any methods to prove similarity of dissolution profiles are accepted as long as they are justified.

The similarity may be compared by model-independent or model-dependent methods e.g. by linear regression of the percentage dissolved at specified time points, by statistical comparison of the parameters of the Weibull function or by calculating a similarity factor e.g the one defined below:

$$f_2 = 50 \bullet \log \left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} \left[\overline{R}(t) - \overline{T}(t)\right]^2}{n}}} \right)$$

In this equation f_2 is the similarity factor, n is the number of time points, R (t) is the mean percent drug dissolved of e.g. a reference product, and T(t) is the mean percent drug dissolved of e.g. a test product.

The evaluation of similarity is based on the conditions of

- A minimum of three time points (zero excluded)
- 12 individual values for every time point for each formulation
- not more than one mean value of > 85% dissolved for each formulation
- that the standard deviation of the mean of any product should be less than 10% from second to last time point.

An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. In cases where more than 85% of the drug are dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation.

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This site is designed help you understand what is involved in participating in clinical research. Before you take part in any study, we encourage you to read the material and be sure that you have satisfactory answers to the list of questions at the end. First decide which of the following categories best describes your situation:

Healthy volunteer:

A volunteer subject with no known significant health problems who participates in research to test a new drug, device, or intervention. A healthy volunteer may be a member of the community, an NIH investigator or other employee, or family members of a patient volunteer. Research procedures with healthy volunteers are designed to develop new knowledge, not to provide direct benefit to study participants.

Healthy volunteers have always played a vital role in medical research. We need to study healthy volunteers for several reasons: When developing a new technique such as a blood test or imaging device, we need healthy volunteers to help us define the limits of "normal." Healthy volunteers are recruited to serve as controls for patient groups. They are often matched to patients on such characteristics as age, gender, or family relationship. They are then given the same test, procedure, or drug the patient group receives. Investigators learn about the disease process by comparing the patient group to the healthy volunteers.

Some studies require a major commitment in time and effort on the part of the volunteer, or they may involve some discomfort. The research procedure may also carry some risk. The consent process for healthy volunteers involves a detailed discussion of all the study's procedures and tests. After this discussion, you will be given a consent document to read that describes the details of the study into which you are considering enrollment. You must read it carefully and sign it only if you understand what is involved and are prepared to accept the potential risk, discomforts, and inconvenience involved.

Patient volunteer:

A volunteer subject with a known health problem, who participates in research to better understand, diagnose, treat, or cure a particular disease or condition. Research procedures with a patient volunteer help develop new knowledge. Such procedures may or may not benefit individual study participants.

The following should help you better understand how the research is planned and carried out, how to weigh the risks, and how your safety and rights are safeguarded.

What is clinical research?

Patient volunteers have a particular illness or condition that can help research doctors and scientists better understand, diagnose, prevent, treat, or cure it. The research is planned to help others and may not benefit you directly. As a patient volunteer, you may be involved in studies similar to those described in the section on healthy volunteers. Benefits of such research may be indirect for you, but may help others.

These studies involve drugs, devices, or interventions designed to prevent, treat, or cure disease. It is important to remember, however, that although such studies may provide direct benefit to patient volunteers, the main aim is to prove, by scientific means, the effects and limitations of the experimental treatment. This may mean that some patients serve as controls by not taking the test drug, or they receive test doses of the drug large enough only to show that it is present, but not at a level that can treat the condition.

What is a clinical trial?

Clinical trials are a means of developing new treatments and medications for diseases and conditions. There are strict rules for clinical trials, which are monitored countrywide by the NIH and the FDA, especially when they involve new drugs. There are three types of study:

The *phase 1 study* is used to learn the "maximum tolerated dose" of a drug that does not produce unacceptable side effects. Patient volunteers are followed primarily for side effects, and not for how the drug affects their disease. The first few volunteer subjects receive low doses of the trial drug to see how the drug is tolerated and to learn how it acts in the body. The next group of volunteer subjects receives larger amounts. Phase 1 studies typically offer little or no benefit to the volunteer subjects.

The *phase 2 study* involves a drug whose dose and side effects are well known. Many more volunteer subjects are tested, to define side effects, learn how it is used in the body, and learn how it helps the condition under study. Some volunteer subjects may benefit from a phase 2 study.

The *phase 3 study* compares the new drug against a commonly used drug. Some volunteer subjects will be given the new drug and some the commonly used drug. The trial is designed to find where new drug fits in the managing a particular condition.

Determining the true benefit of a drug in a clinical trial is difficult. Medical research is dogged by the "placebo effect"--the real or apparent improvement in a patient's condition due to wishful thinking by the investigator or the patient. Medical techniques use three ways to rid clinical trials of this problem. These methods have helped discredit some previously accepted treatments and validate new ones. Methods used are the following: randomization, single-blind or double-blind studies, and the use of a placebo.

Randomization is when two or more alternative treatments are selected for you by chance, not by choice. The treatment chosen is given with the highest level of professional care and expertise and the results of each treatment are compared. Analyses are done at intervals during a trial, which may last years. As soon as one treatment is found to be definitely superior, the trial is stopped. In this way, the fewest number of patients receive the less beneficial treatment.

In *single-or double-blind studies,* the participants don't know which medicine is being used, and they can describe what happens without bias. Blind studies are designed to prevent anyone (doctors, nurses, or patients) from influencing the results. This allows scientifically accurate conclusions. In single-blind ("single-masked") studies, only the patient is not told what is being given. In a double-blind study, only the pharmacist knows; the doctors, nurses, patients, and other health care staff are not informed. If medically necessary, however, it is always possible to find out what the patient is taking.

Placebos are harmless, inactive substances made to look like the real medicine used in the clinical trial. Placebos

allow the investigators to learn whether the medicine being given works better or no better than ordinary treatment. In many studies, there are successive time periods, with either the placebo or the real medicine. In order not to introduce bias, the patient, and sometimes the staff, are not told when or what the changes are. If a placebo is part of a study, you will always be informed in the consent form given to you before you agree to take part in the study.

When you read the consent form, be sure that you understand what research approach is being used in the study you are entering. Remember, even with a clinical trial, there is no guarantee that the new approach will be effective for you.

Are there risks involved in participating in clinical research?

Risks are involved in clinical research, as in routine medical care and activities of daily living. In thinking about the risks of research, it is helpful to focus on two things: the degree of harm that could result from taking part in the study, and the chance of any harm occurring. Most clinical studies pose risks of minor discomfort, lasting only a short time. Some volunteer subjects, however, experience complications that require medical attention. In rare cases, volunteer subjects have received serious injuries or died of complications resulting from their participation in trials of experimental therapies.

The specific risks associated with any research protocol are described in detail in the consent document, which you are asked to sign before taking part in research. In addition, the major risks of participating in a study will be explained to you by a member of the research team, who will answer your questions about the study. Before deciding to participate, you should carefully weigh these risks. Although you may not receive any direct benefit as a result of participating in research, the knowledge developed may help others. The following section describes safeguards to protect the safety and rights of volunteer subjects.

How are my rights safeguarded?

Protocol review

As in any medical research facility, all new protocols produced at NIH must be approved by an institutional review board (IRB) before they can begin. The IRB, which consists of medical specialists, statisticians, nurses, social workers, and medical ethicists, is the advocate of the volunteer subject. The IRB will only approve protocols that address medically important questions in a scientific and responsible manner.

Informed consent

Your participation in any Clinical Center research protocol is voluntary. For every study in which you intend to participate, you will receive a document called "Consent to Participate in a Clinical Research Study" that explains the study in straightforward language. A member of the research team will discuss the protocol with you, explain its details, and answer your questions. Reading and understanding the protocol is your responsibility. You may discuss the protocol with family and friends. You will not be hurried into making a decision, and you will be asked to sign the document only after you understand the nature of the protocol and agree to the commitment. At any time after signing the protocol, you are free to change your mind and decide not to participate further. This means that you are free to withdraw from the study completely, or to refuse particular treatments or tests. Sometimes, however, this will make you ineligible to continue the study. If you are no longer eligible or no longer wish to continue the study, you will return to the care of the doctor who referred you to NIH.

Patient representative

The patient representative acts as a link between the patient and the hospital. The patient representative makes every effort to assure that patients are informed of their rights and responsibilities, and that they understand what the Clinical Center is, what it can offer, and how it operates. We realize that this setting is unique and may generate questions about the patient's role in the research process.

As in any large and complex system, communicating can be a problem and misunderstandings can occur. If you have an unanswered question or feel there is a problem you'd like to discuss, call the patient representative. The sooner your concerns are known, the easier they are to address.

Bill of Rights

Finally, whether you are a healthy or a patient volunteer subject you are protected by a bill of rights drawn up by the American Hospital Association for use in all hospitals in the country. The bill of rights concerns the care you receive, privacy, confidentiality, and access to medical records.

Questions to ask before agreeing to participate in a research protocol:

What is the purpose of the study?

What is required of me?

What is my role in the study-am I a healthy volunteer or a patient volunteer?

Will the study directly benefit me?

Will the study benefit others?

Are there risks? If so, what are they and what are the chances that they will occur?

What discomforts are involved?

What is the total time involved?

Are there other inconveniences?

Have I discussed participation in the study with those who are important to me, such as family and friends?

Do I wish to participate in this study?

For more information about the Clinical Center, contact CC Communications (OCCC@NIH.GOV) or call (301)-496-2563.

For more information on participating in research, contact the Patient Recruitment and Public Liason Office, prpl@cc.nih.gov or call 1-800-411-1222.

***Source of above information: NIH, USA

21965
Ser. No. 09/890,029

Patient Information Publications

NIH Clinical Center
National Institutes of Health

Partners in Research
Volunteer Patients and the Clinical Center

The National Institutes of Health (NIH) is one of the nation's foremost centers for bio - medical research. NIH is divided into an extramural part, which handles biomedical research throughout the country, and an intramural part, based mainly in Bethesda, Maryland. NIH is composed of various Institutes, each of which conducts research on health and disease. Studies involving vol - unteer subjects (research patients and clini - cal research volunteers) are carried out in the Warren Grant Magnuson Clinical Center.

The Clinical Center is the Federal govern - ment's premier biomedical research hospital, where clinical studies of the highest quality are performed. Because the research is fund - ed by the Federal government, there is no cost for care received at the Clinical Center.

Volunteer subjects at the Clinical Center become partners in a special relationship with members of the research teams in the search for better ways to treat disease.

What does it mean to be a volunteer?

The health of millions has been improved because of advances in science and technology, and the willingness of thousands of individuals like you to take part in clinical research. The role of volunteer subjects as partners in clinical research is crucial in the quest for knowledge that will improve the health of future generations. Without your help, the research studies at the Clinical Center cannot be accomplished.

This information is prepared to help you understand what is involved in participating in clinical research. Before you take part in any study, we encourage you to read the booklet and be sure that you have satisfactory answers to the list of questions on the last page. First decide which of the following categories best describes your situation:

- *Clinical research volunteer:* A volunteer subject with no known significant health problems who participates in research to test a new drug, device, or intervention. The clinical research volunteer may be a member of the community, an NIH investigator or other employee, or family members of a patient volunteer. Research procedures with these volunteers are designed to develop new knowledge, not to provide direct benefit to study participants.

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Some studies require a major commitment in time and effort on the part of the volunteer, or they may involve some discomfort. The research procedure may also carry some risk. The consent process for clinical research volunteers involves a detailed discussion of all the study's procedures and tests. After this discussion, he or she will be given a consent document to read. This document details the study being considered. It must be read carefully and signed only when the clinical research volunteer understands what is involved and is prepared to accept the potential risk, discomforts, and inconvenience involved.

- *Patient volunteer:* A volunteer subject with a known health problem, who participates in research to better understand, diagnose, treat, or cure a particular disease or condition. Research procedures with a patient volunteer help develop new knowledge. Such procedures may or may not benefit individual study participants.

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At any time after signing the consent document, you are free to change your mind and decide not to participate further. This means that you are free to withdraw from the study completely, or to refuse particular treatments or tests. Sometimes, however, this will make you ineligible to continue the study. If you are no longer eligible or no longer wish to continue the study, you will return to the care of the doctor who referred you to NIH.

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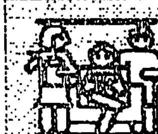
As in any large and complex system, communication can be a problem and misunderstandings can occur. If you have an unanswered question or feel there is a problem you'd like to discuss, call the Patient Representative. The sooner your concerns are known, the easier they are to address.

Bill of Rights

Finally, whether you are a clinical research or a patient volunteer subject, you are protected by the Clinical Center Patients' Bill of Rights. This document is adapted from the one made by the American Hospital Association for use in all hospitals in the country. The bill of rights concerns the care you receive, privacy, confidentiality, and access to medical records. Your patient handbook contains this information.

Questions to ask before agreeing to participate in a research protocol

1. What is the purpose of the study?
2. What is required of me?
3. What is my role in the study—am I a clinical research volunteer or a patient volunteer?
4. Will the study directly benefit me?
5. Will the study benefit others?
6. Are there risks? If so, what are they and what are the chances that they will occur?
7. What discomforts are involved?
8. What is the total time involved?
9. Are there other inconveniences?
10. Have I discussed participation in the study with those who are important to me, such as family and friends?
11. Do I wish to participate in this study?
12. When can I decide not to participate in all or part of the study? What will be the consequences?



2005

This information is prepared specifically for patients participating in clinical research at the Warren Grant Magnuson Clinical Center at the National Institutes of Health and is not necessarily applicable to individuals who are patients elsewhere. If you have questions about the information presented here, talk to a member of your healthcare team.

Where applicable, brand names of commercial products are provided only as illustrative examples of acceptable products, and do not imply endorsement by NIH, nor does the fact that a particular brand name product is not identified imply that such product is unsatisfactory.

National Institutes of Health
NIH Clinical Center
Bethesda, MD 20892

Questions about the Clinical Center?
OCCC@cc.nih.gov

21965
Ser. No. 09/890,029

(http://www.open.mis.surrey.ac.uk/misweb/modules/7431.htm)

FULL MODULE DESCRIPTION

Module Name : ***Short***	PGMSCPM11	***Module Title :***	Conducting studies in non-patient volunteers

Objectives/Learning Outcomes

The objective of this module is to provide the candidate with a broad understanding of legal, ethical and moral requirements for conducting studies in health human volunteers, including appropriate facilities, equipment and staff. The medical examinations of a healthy subject appropriate prior to drug administration and the most common adverse effects and their prevention/management will be reviewed.

Content

- National and international legal requirements and guidelines
- Ethics of volunteer studies
- Informed consent
- Staff training and experience
- Appropriate facilities
- Common adverse reactions and the management of acute medical emergencies
- Definition of a healthy volunteer (appropriate pre-study test and considerations of the limits of 'normality' for laboratory data, cardiovascular data)
- Assessing animal toxicology and pharmacokinetics data
- Design of healthy volunteer studies
- Conduct of studies with radiolabelled drugs
- Studies in special population (young, elderly, pre and post menopausal women)
- Drug interactions

Prerequisites

Module 1

Pattern of Delivery

3 continuous days of contact for a minimum of 24hrs followed by self directed learning and written assignments for a minimum of 76hrs (100 hours of study per module)

Methods of Teaching/Learning

There are a number of lecture type presentations with some group exercises

Methods of Assessment and Weighting

A variety of problem based exercises that require personal research and study to answer.

Selected Texts

- Eds. Cutler, R., Sramek, J.J. & Narang, P.K. 1994, *Pharmacodynamics and Drug Development, Perspectives in Clinical Pharmacology*, John Wiley ISBN 0-471-95052-1
- Eds. Close, B., Combes, R., Hubbard, A. & Illingworth, J. 1997, *Volunteers in Research and Testing*, Taylor & Francis ISBN 0-7484-0397-3
- Eds. O'Grady, J. & Linet, O. 1990, *Early Phase Drug Evaluation In Man*, Macmillan Press ISBN 0-333-48732-X
- Eds. O'Grady, J. & Joubert, P.H. 1997, *Handbook of Phase I/II Clinical Trials*, CRC Press ISBN 0-8493-9230-5

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Ser. No. 09/890,029 Enclosure 1

U.S. Food and Drug Administration

Equality In Clinical Trials Drugs and Gender

by Judith Levine Willis FDA Consumer Special Report

Women woke up almost twice as fast from anesthesia as men in a study reported at the annual meeting of the American Society of Anesthesiologists, in October 1996. In another recent study, the class of painkillers called kappa opoioids seemed to work about twice as well for women as for men. These are but two of a growing number of clinical studies providing new information about possible differences in ways women and men respond to drugs.

Reporting on the anesthesia study, one of the researchers, Peter S. Glass of Duke University Medical Center, said the gender finding emerged unexpectedly during a study of how management of anesthetic drugs during surgery influences recovery time from general anesthesia. The study included 300 people. Women took an average of seven minutes to emerge from anesthesia, while men took 13. The difference occurred independently of differences in body weight.

In the painkiller study, according to a report published in the November 1996 issue of *Nature Medicine*, women having wisdom teeth removed had a better and longer response to these drugs than men, even when factors such as body size and menstrual cycle were considered.

Until recently, women were not routinely included in many human trials to determine whether drugs are safe and effective. The reason usually given was that excluding women protected them, since there was often no way to be sure that a woman was not pregnant or that the drug might not cause some problem that might interfere with future pregnancies. In addition, it was thought that women's hormonal cycling or other factors peculiar to being female might constitute variables that could skew trial results.

However, over the last several years, research has accumulated indicating that drug results from male-only trials may not apply equally to women, or may not give data on effects important to women. At one time, researchers thought most of the differences between the way men and women reacted to drugs might be attributed to differences in height, weight and hormones. This meant, for example, that simply because most men weigh more than most women, most men would be able to tolerate higher doses of medications without side effects. Today many scientists think it's far more complicated. For example, the liver may be different enough in men and women to account for at lease part of why most women seem to metabolize drugs differently than men. And in the case of pain relief, there may be gender differences in pain tolerance and differences in the way each gender responds to various pain medications.

The rising recognition of these and other gender factors has brought changes in the way the Food and Drug Administration asks firms to test drugs and in the data the agency asks them to provide.

For example, in September 1995 FDA proposed to amend its investigational and new drug regulations to require drug sponsors to include data about gender, as well as age and race. The proposal does not require manufacturers to conduct additional studies. Rather, the manufacturers would simply provide information previously gathered in a new, more useful, format.

FDA suggested changes of this nature in 1993 as a revision to a 1977 Guideline, "General Considerations for Clinical Evaluation of Drugs, " after the agency found that few women were included in the earliest stages of drug clinical trials. In addition, the agency found that there had been little study of the effects on drug action of such factors as the menstrual cycle, menopause, and hormone use. The 1993 guideline left gender analysis voluntary; it was not a requirement.

Subsequent studies by FDA and the General Accounting Office have shown that women are often included in later phases of clinical trials, and are included in proportions similar to the proportion of women who have the condition the drug is being tested for. But FDA believes

that inclusion alone is not enough. What is needed, in addition, is an effort to use data from the trials to discover potential gender differences.

Impact of HIV

Rachel Behrman, M.D., supervisory medical officer in FDA's division of antiviral drug products, says the issues surrounding these changes were brought to the forefront by efforts to treat HIV (the virus that causes AIDS) in women.

"The guidelines always provided that women with serious or life-threatening diseases could obtain an experimental drug in early phases of testing," say Behrman. "What's new is that now we're saying to drug manufacturers, 'Not only do we recommend that you study it in women, we may insist that you do so, if it's going to be used by women who have serious and life-threatening diseases.'"

She explains that because of the urgent need, drug testing for HIV is on a fast track, with condensed stages of controlled studies and, frequently, fewer people in them.

"Since the process moves so quickly, extensive clinical data collected over a long period of time often are not available," she says. "You need to know as soon as possible, for example, what adverse effects occur that might be dose-dependent, and work up those differences early in the drug development program. You don't want to wait for later stages of testing to begin to define dosage adjustments for men and women."

Many researchers feel the reason for including women in any phase 1 drug trial — regardless of the seriousness of the disease --- should be to provide important data about the drug. This data includes whether women in general absorb, metabolize or excrete the drug differently from men, or have different reactions to the drug.

Early in the AIDS epidemic, very few women with HIV were included in studies. But their numbers are increasing. According to the National Institute of Allergy and Infectious Diseases (NIAID), in 1995 women accounted for 16.2 percent of adult participants in the AIDS Clinical Trials Group, the institute's largest clinical trials network. That percentage is up from 7 percent in 1988 and 8.4 percent in 1991.

In a study by FDA's Behrman, Kimberly Struble, Theresa Toigo and Debra Birnkrant, 136 of 156 clinical studies of HIV treatment conducted between 1988 and 1994 enrolled women. And, even in the 20 trials that did not include women, enrollment of women — including those of childbearing ages — was permitted. Enrollment of women in the other trials ranged up to 64 percent, with a mean of 11.6 percent.

Some HIV studies include only women. Better information on the length of survival and quality of life in HIV-infected women are research goals of the Women's Interagency HIV Study, conducted by the Centers for Disease Control and Prevention and NIAID. This large-scale study is designed to identify clinical signs of HIV infection in women, describe how the immune system declines, and look for factors that can affect the progression of the disease. It will also examine factors influencing women's access to health care.

Other NIAID-sponsored studies center on pregnancy and HIV. They are designed to examine the effect of antiviral drug treatment on both the mother and fetus, the influence of HIV on pregnancy, and the effects of pregnancy on the course of HIV infection. In addition, two experimental vaccines are being tested in pregnant women who are infected with HIV but are otherwise healthy. Phase 1 studies focus primarily on safety, but will also evaluate the vaccines' potential to reduce the amount of virus in the mother and to stimulate antibodies that will prevent infection of the fetus.

In August 1994, FDA approved the antiviral Retrovir (zidovudine, or AZT) to help prevent maternal-fetal transmission of HIV. A study of the drug for this use was halted early when preliminary data showed extremely encouraging results; that 8.3 percent of babies born to HIV-infected pregnant women treated with the drug became infected, compared with 25.5 percent of babies born to women on placebo.

Marian Segal also contributed to this article.

Your Guide to Women's Health, Third Edition, an FDA Consumer Special Report, September 1997. http://www.fda.gov/oashi/aids/equal.html

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Ser. No. 09/890,029 Enclosure 2

J Chromatogr. 1986 Oct 31;382:247-52.
Analysis of homocysteine in human urine using high-performance liquid chromatography with electrochemical detection.

Thomson SB, Tucker DJ.

PIP: This report describes the modifications made to the analytical system prior to determination of homocysteine in human urine. It also contains data which compare the homocysteine concentrations in the urine of males and females as well as the results of a study in which the effect of oral contraceptive (OC) use by a group of women upon their urinary concentrations was compared to a control group. Furthering this work, the effect of cigarette smoking on the urinary homocysteine concentrations of OC users as compared to control was assessed as were the urinary homocysteine concentrations over a 28-day collection period for both an OC-using female and a male volunteer. 2 M perchloric acid (AR grade, Ajax Chemicals) was used to prevent thiol group oxidation. Approximately 50 ml of urine flow from volunteers participating in this study were collected into vessels containing 10 ml of 2M perchloric acid. In all cases the samples were obtained in the morning immediately upon waking, and for the comparison of OC users with controls, the urine samples were obtained on the 21st day of their cycle. Homocysteine was quantified by the standard addition technique using peak-height measurement, the determination being carried out in triplicate. The homocysteine concentration then was expressed per mg creatinine. All the study participants were apparently healthy with an average age in the mid-20s for the femles and the late 20s for the males. The significantly higher excretion rate of homocysteine for the males compared with the females was of interest since the risk of myocardial infarction for males is up to 6 times greater than for females in the under 40 age bracket. Neither OC formulation caused an increase in the excreted level of homocysteine in the urine of users as compared to the control group. It seems that the increased incidence of thrombotic episodes observed among women using OCs as compared to controls was due to a cause other than an elevated homocysteine level caused by the synthetic steroid components of the OC formulation. The similarity of homocysteine excretion levels in the urine of smoking and nonsmoking OC users suggests that smoking most likely increases the risks associated with OC, including that of developing thrombosis. Other results show that any homocysteine urinary excretion changes which might follow the estrogen pattern of a triphasic OC formulation during a cycle would appear to be impossible to detect. This is because dietary effects, among other things, may cause sufficiently large changes in the level of homocysteine excreted in the urine to mask any effects upon the excretion rate that hormonal changes might produce.

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Plasma homocysteine in women on oral oestrogen-containing contraceptives and in men with oestrogen-treated prostatic carcinoma.

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The mechanism by which oral oestrogen-containing contraceptives in women and oestrogen treatment of prostatic carcinoma in men increases the risk of vascular disease is unclear. These agents decrease serum concentrations of vitamin B12, pyridoxal 5-phosphate, and folate, all of which are essential for the metabolism of the atherogenic amino acid homocysteine. We found serum vitamin B12 concentrations to be lower in 17 women using oral contraceptives (219 +/- 84 pmol l-1) than in 13 age-matched female controls (385 +/-

129, p less than 0.001), but similar values were obtained in the two groups both for fasting plasma homocysteine concentrations (9.1 +/- 2.4 vs 9.2 +/- 3.6 mumol l-1) and for the increase in these concentrations after methionine loading (19.2 +/- 7.5 vs 17.8 +/- 5.2 mumol l-1). In five men with prostatic carcinoma, high-dose oestrogen treatment decreased serum vitamin B12 concentrations by a mean of 30% (p less than 0.05) within 4 weeks, during which fasting plasma homocysteine concentrations decreased (13.8 +/- 4.5 vs 10.5 +/- 2.8 mumol l-1) and response to methionine loading increased (12.4 +/- 3.4 vs 17.3 +/- 5.1 mumol l-1), though the latter changes were non-significant. Our findings do not support the hypothesis that hyperhomocysteinemia explains cardiovascular risk in women using oral oestrogen-containing contraceptives, or in oestrogen-treated men with prostatic carcinoma.

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Hormone replacement therapy and plasma homocysteine levels.

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OBJECTIVE: To compare the effects of 4 and 12 weeks of combined estradiol-progestogen replacement with unopposed estradiol therapy on fasting plasma total homocysteine concentrations in healthy postmenopausal women. METHODS: In this prospective, 12-week study in healthy postmenopausal women, we randomly assigned 59 women to sequentially combined daily 2 mg estradiol (E2) plus either trimegestone 0.5 mg daily or dydrogesterone 10 mg daily (n = 28), or to unopposed daily 2 mg estradiol (n = 16), or to placebo (n = 15). RESULTS: Fasting plasma total homocysteine concentrations decreased by 9.4% in the combined estradiol-progestogen group and by 5.1% in the estradiol-only group, and they increased by 2.4% in the placebo group (analysis of covariance: combined hormone replacement therapy compared with placebo (P = .02); combined therapy compared with estradiol (P = .23); and estradiol compared with placebo (P = .26). Reductions were detectable after 4 weeks of combined estradiol-progestogen treatment. The data suggest an additional progestogen-related reduction in homocysteine levels of 0.7 micromol/L and 0.4 micromol/L after 4 and 12 weeks, respectively. Women with a baseline homocysteine concentration in the highest quartile had significantly greater reductions in homocysteine compared with women with an initial homocysteine value in the lowest quartile. CONCLUSION: Fasting total homocysteine concentrations were significantly reduced by combined estradiol-progestogen replacement. Women with high homocysteine levels at baseline benefit the most. The progestogens used in this study did not have an unfavorable effect on homocysteine metabolism.
